(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 April 2004 (01.04.2004)

PCT

(10) International Publication Number
WO 2004/026229 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US2003/027491

(22) International Filing Date: 3 September 2003 (03.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/408,029 4 September 2002 (04.09.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PYRAZOLOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

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NOVEL PYRAZOLOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBITORS

Field of the Invention

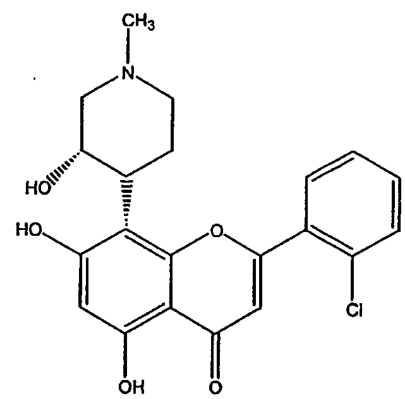
The present invention relates to pyrazolo[1,5-a]pyrimidine compounds useful as protein kinase inhibitors, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, and fungal diseases. This application claims benefit of priority from U.S. provisional patent application Serial No. 60/408,029 filed September 4, 2002.

Background of the Invention

The cyclin-dependent kinases (CDKs) are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Individual CDK's, such as, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK7, CDK8 and the like, perform distinct roles in cell cycle progression and can be classified as either G1, S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer cells, and misregulation of CDK function occurs with high frequency in many important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. Checkpoints serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorgenesis. The CDK2 pathway influences tumorgenesis at the level of tumor suppressor function (e.g. p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator, cyclin E, and the inhibitor, p27, of CDK2 are either over – or underexpressed, respectively, in breast, colon, nonsmall cell lung, gastric, prostate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased CDK2 activity levels and poor overall survival. This observation makes CDK2 and its regulatory

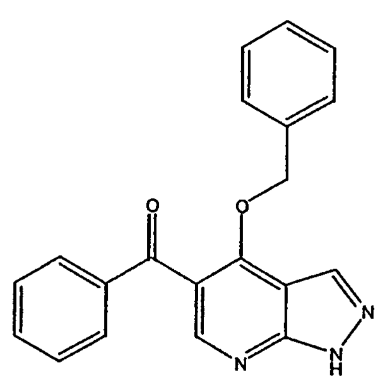
pathways compelling targets for the development years, a number of adenosine 5'-triphosphate (ATP) competitive small organic molecules as well as peptides have been reported in the literature as CDK inhibitors for the potential treatment of cancers. U.S. 6,413,974, col. 1, line 23- col. 15, line 10 offers a good description of the various CDKs and their relationship to various types of cancer.

CDK inhibitors are known. For example, flavopiridol (Formula I) is a nonselective CDK inhibitor that is currently undergoing human clinical trials, A. M. Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.



Formula I

Other known inhibitors of the CDKs include, for example, olomoucine (J. Vesely *et al*, *Eur. J. Biochem.*, (1994) 224, 771-786) and roscovitine (I. Meijer *et al*, *Eur. J. Biochem.*, (1997) 243, 527-536). U.S. 6,107,305 describes certain pyrazolo[3,4-b] pyridine compounds as CDK inhibitors. An illustrative compound from the '305 patent has the Formula II:



Formula II

K. S. Kim *et al, J. Med. Chem.* 45 (2002) 3905-3927 and WO 02/10162 disclose certain aminothiazole compounds as CDK inhibitors.

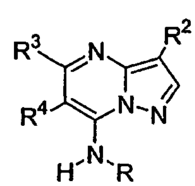
Pyrazolopyrimidines are known. For Example, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem. Pharm. Bull., (1962)* 10 620 disclose various pyrazolopyrimidines.

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with CDKs. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

Summary of the Invention

In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula III:



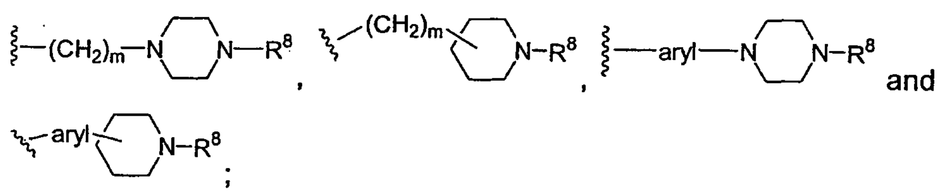
Formula III

wherein:

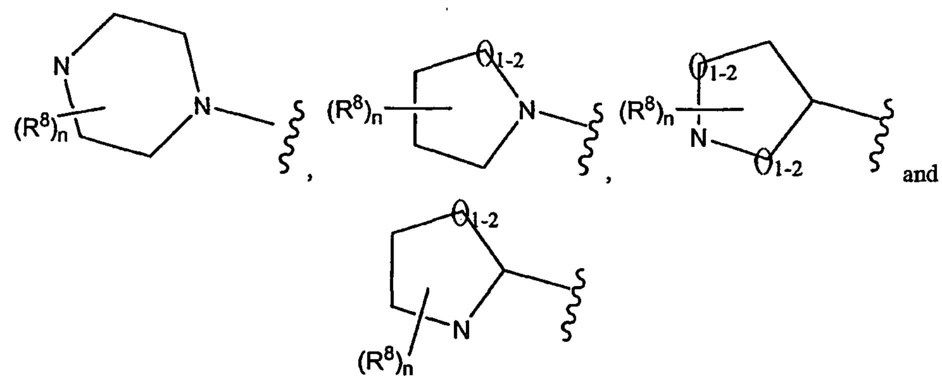
R is an unsubstituted aryl or aryl substituted with one or more moieties which moieties can be the same or different, each moiety being independently selected from the group consisting of halogen, CN, $-OR^5$, SR^5, $-CH_2OR^5$, $-C(O)R^5$,

-SO_3H, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -NR^5R^6, -$C(O)NR^5R^6$, -CF_3, -OCF_3 and heterocyclyl;

R^2 is selected from the group consisting of R^9, alkyl, alkynyl, alkynylalkyl, cycloalkyl, -CF_3, -$C(O_2)R^6$, aryl, arylalkyl, heteroarylalkyl, heterocyclyl, alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected, aryl substituted with 1-3 aryl or heteroaryl groups which can be the same or different and are independently selected from phenyl, pyridyl, thiophenyl, furanyl and thiazolo groups,



R^3 is selected from the group consisting of H, halogen, -NR^5R^6, -$C(O)NR^5R^6$, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl,



wherein each of said alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl for R^3 and the heterocyclyl moieties whose structures are shown immediately above for R^3 can be substituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, -OCF_3, -$(CR^4R^5)_nOR^5$, -OR^5, -NR^5R^6, -$(CR^4R^5)_nNR^5R^6$, -$C(O_2)R^5$, -$C(O)R^5$, -$C(O)NR^5R^6$, -SR^6, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ and -$N(R^5)C(O)NR^5R^6$;

R^4 is H, halo or alkyl;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-N(R^5)Boc$, $-(CR^4R^5)_nOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

R^{10} is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^4R^5$, $-N(R^5)Boc$, $-(CR^4R^5)_nOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^4R^5$;

or optionally (i) R^5 and R^{10} in the moiety $-NR^5R^{10}$, or (ii) R^5 and R^6 in the moiety $-NR^5R^6$, may be joined together to form a cycloalkyl or heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with one or more R^9 groups;

R^7 is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ and $-N(R^5)C(O)NR^5R^{10}$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^{10}$,

$-S(O_2)NR^5R^{10}$, $-C(O)R^7$ and $-S(O_2)R^7$;

R^9 is selected from the group consisting of halogen, CN, $-NR^5R^{10}$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

m is 0 to 4, and

n is 1 to 4,

with the following provisos: (i) that when R is an unsubstituted phenyl, then R^2 is not alkyl, $-C(O_2)R^6$, aryl or cycloalkyl, and (ii) that when R is a phenyl substituted with a hydroxyl group, then R^2 is halogen only.

The compounds of Formula III can be useful as protein kinase inhibitors and can be useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

Detailed Description

In an embodiment, the present invention discloses pyrazolo[1,5-a]pyrimidine compounds which are represented by structural Formula III, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

In another embodiment, R is an unsubstituted aryl or aryl substituted with one or moieties which moieties can be the same or different with each moiety being independently selected from the group consisting of halogen, CN, $-OR^5$, $-S(O_2)NR^5R^6$, $-SO_3H$, CH_2OR^5, $-S(O_2)R^6$, $-C(O)NR^5R^6$, $-CF_3$, $-OCF_3$ and heterocyclyl.

In another embodiment, R^2 is halogen, CF_3, CN, lower alkyl and cycloalkyl.

In another embodiment, R^3 is H, unsubstituted aryl, unsubstituted heteroaryl, aryl substituted with one or more moieties selected from the group consisting of halogen, CN, $-OR^5$, CF_3, $-OCF_3$, lower alkyl and cycloalkyl, heteroaryl substituted with one or more moieties selected from the group consisting of halogen, CN, $-OR^5$, CF_3, $-OCF_3$, alkyl and cycloalkyl, and heterocyclyl.

In another embodiment, R^4 is H or lower alkyl.

In another embodiment, R^5 is H or lower alkyl.

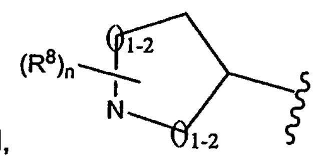
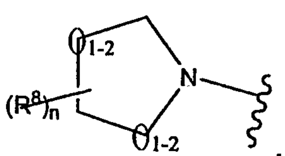
In another embodiment, n is 1 or 2.

In an additional embodiment, R is unsubstituted phenyl.

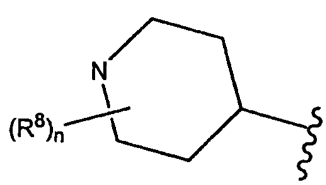
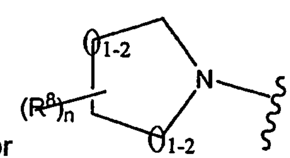
In an additional embodiment, R is phenyl substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, $-SO_3H$, $-S(O_2)NR^5R^6$, $-S(O_2)CH_3$, -OH, CF_3 and morpholinyl.

In an additional embodiment, R^2 is F, Cl, Br, CF_3, lower alkyl, cyclopropyl, cyclobutyl or cyclopentyl.

In an additional embodiment, R^3 is H, aryl wherein said aryl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Cl, Br, CF_3, lower alkyl, methoxy and CN,
alkyl, heteroaryl, heterocyclyl or heterocyclyl substituted with at least one hydroxyalkyl.

In an additional embodiment, R^3 is 2-fluorophenyl, 2-chlorophenyl, 2,3-dichlorophenyl, 2-methylphenyl, 2-methoxyphenyl,  or  .

In an additional embodiment, R^3 is:

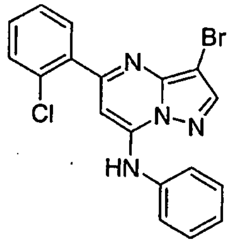
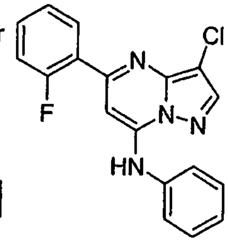
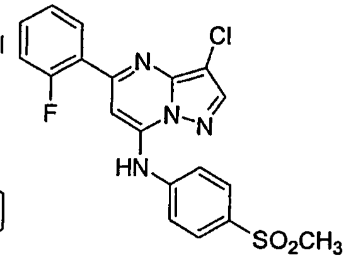
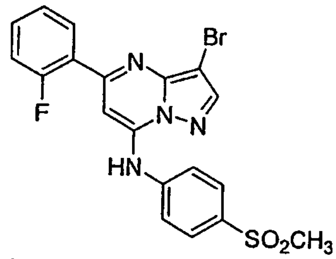
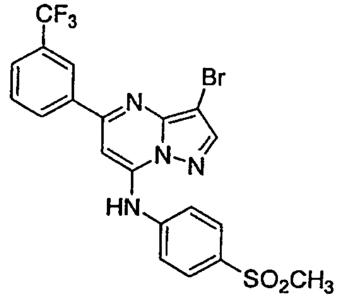
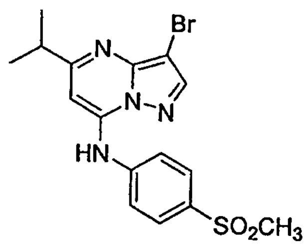
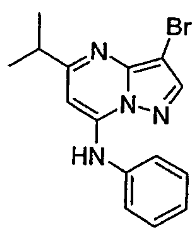
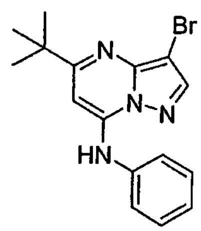
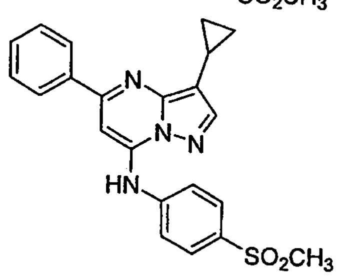
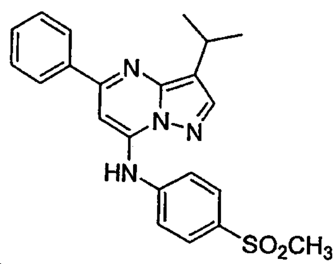
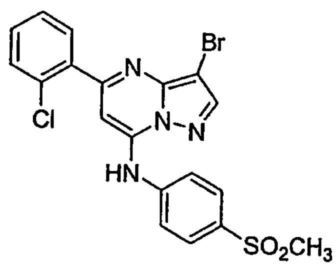
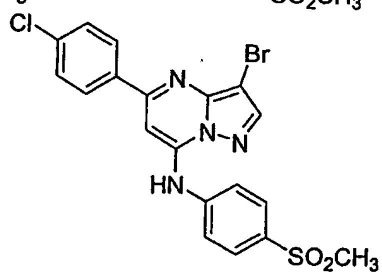
 or  ,

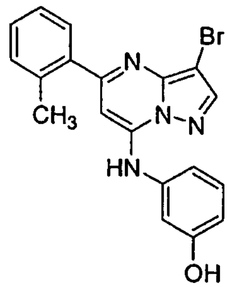
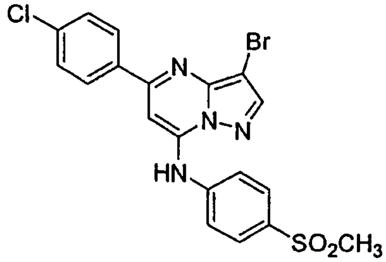
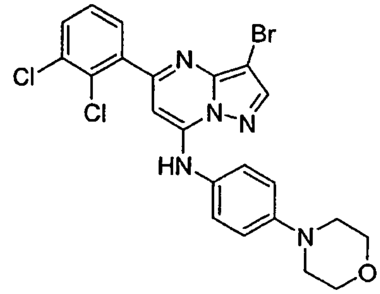
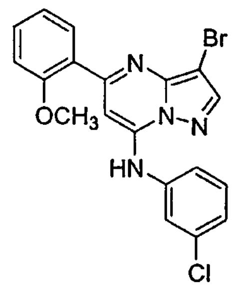
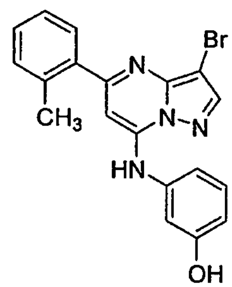
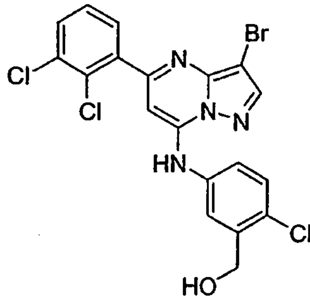
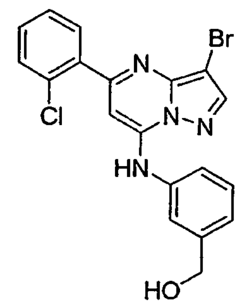
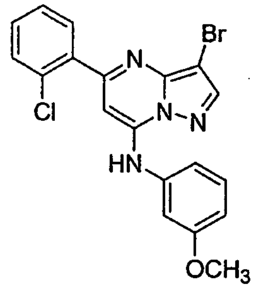
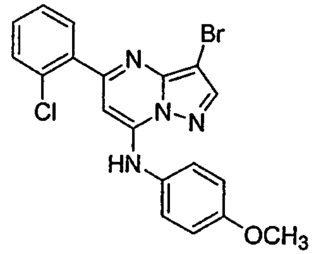
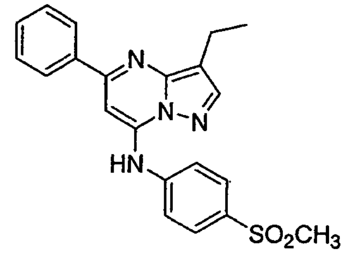
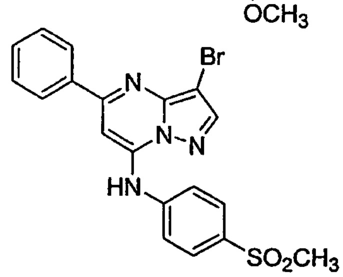
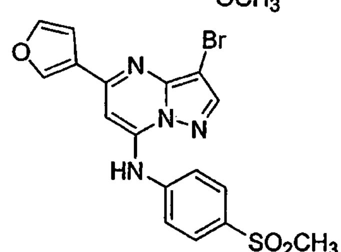
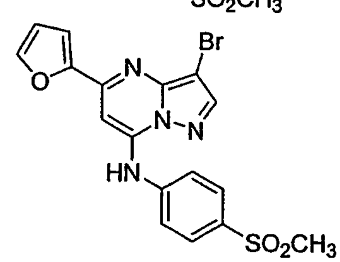
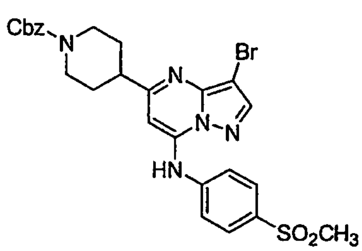
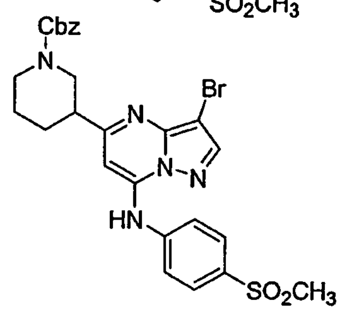
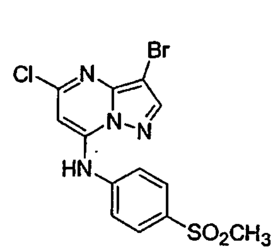
In an additional embodiment, R^4 is H.

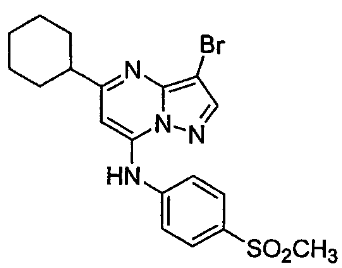
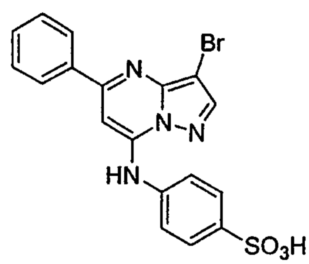
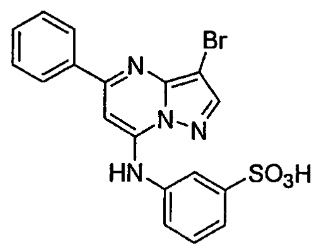
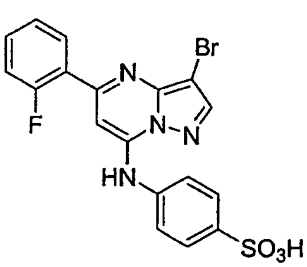
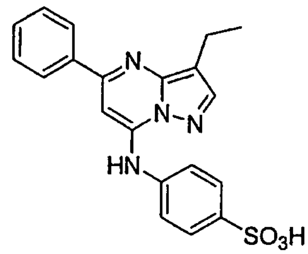
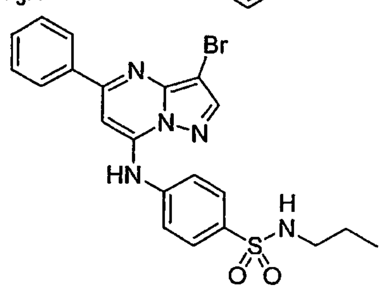
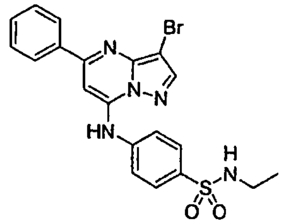
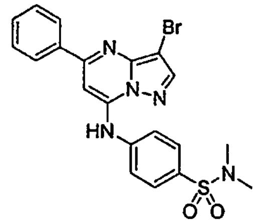
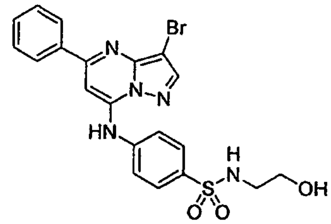
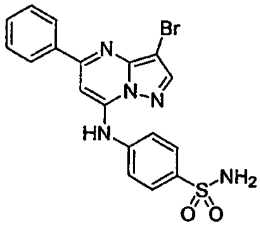
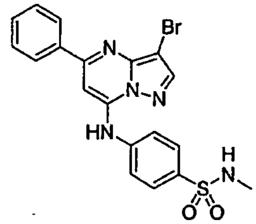
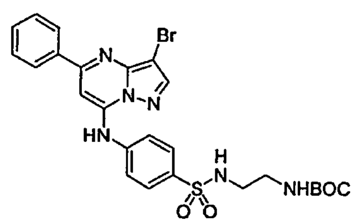
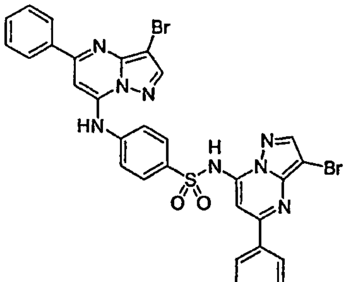
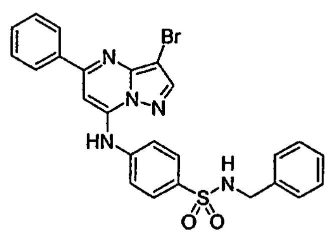
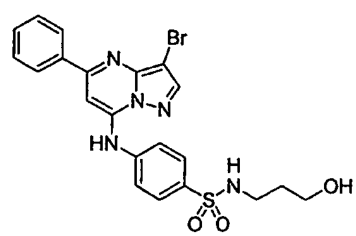
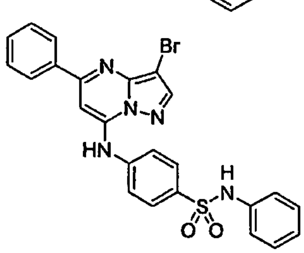
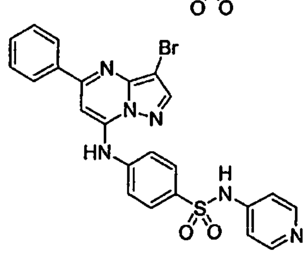
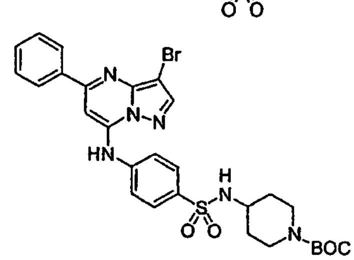
In an additional embodiment, R^5 is H.

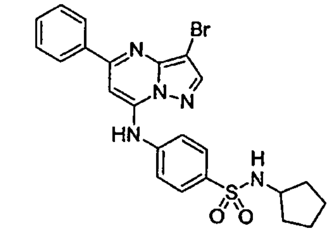
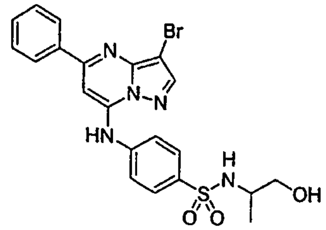
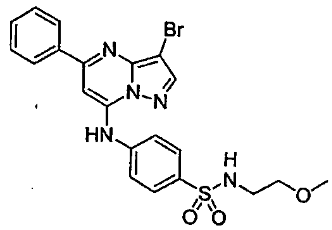
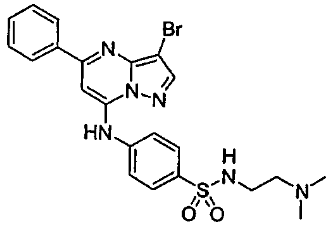
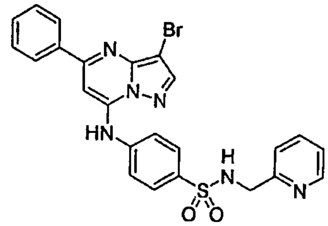
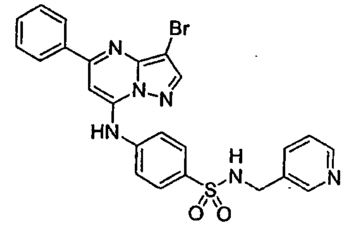
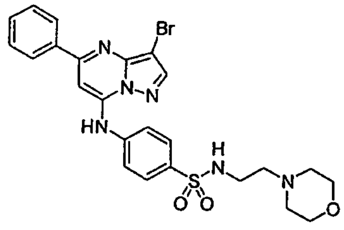
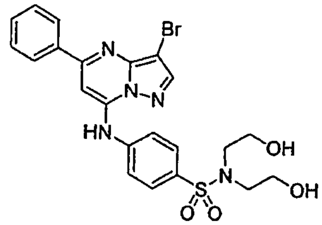
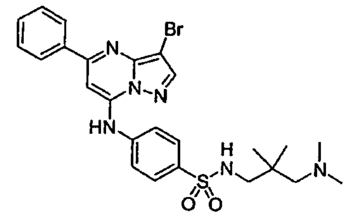
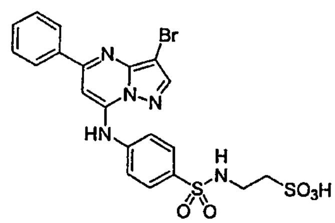
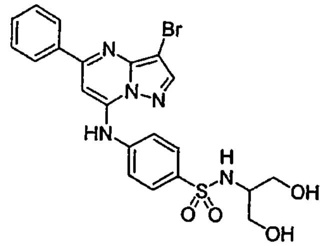
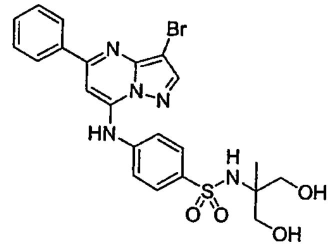
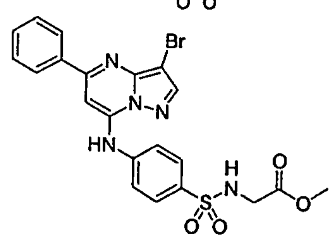
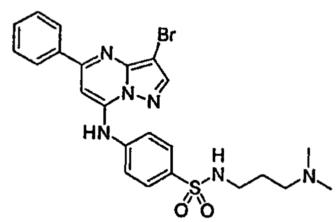
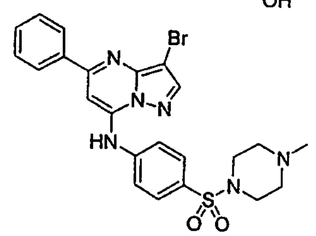
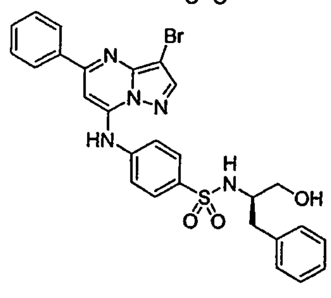
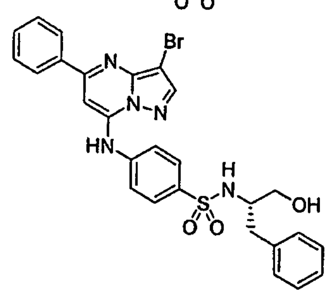
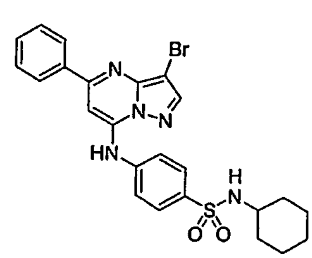
An inventive group of compounds are shown in **Table 1**.

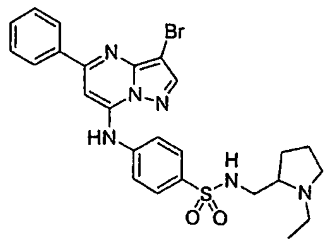
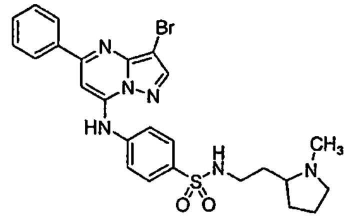
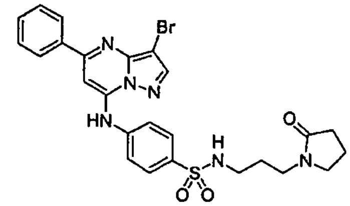
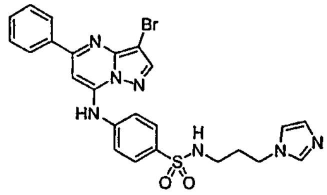
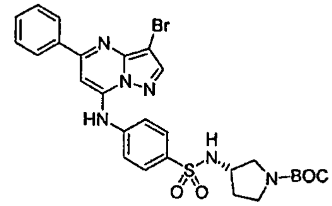
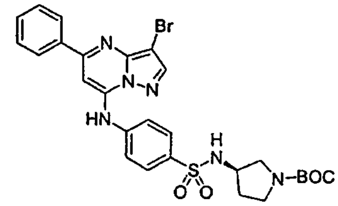
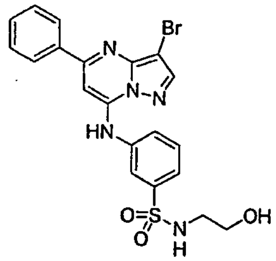
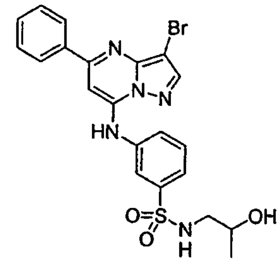
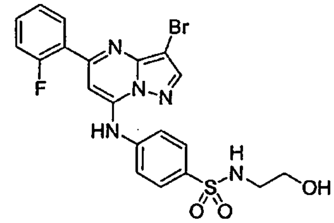
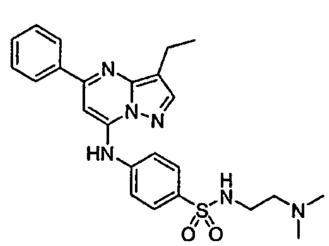
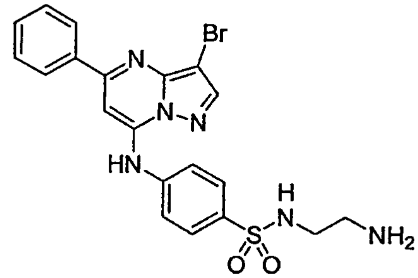
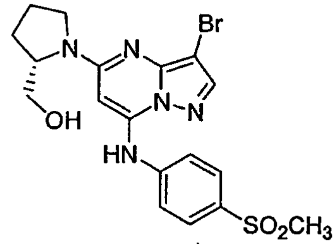
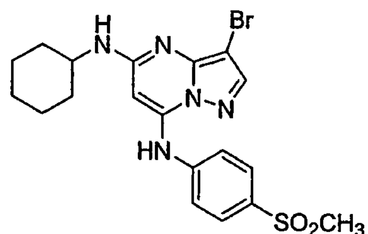
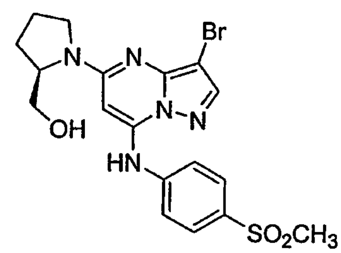
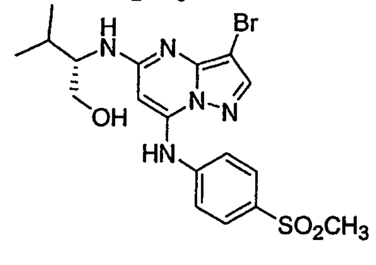
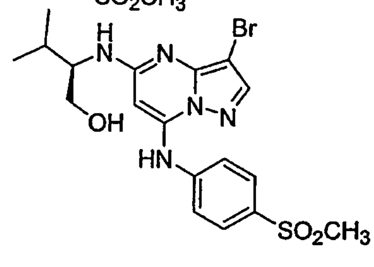
Table 1

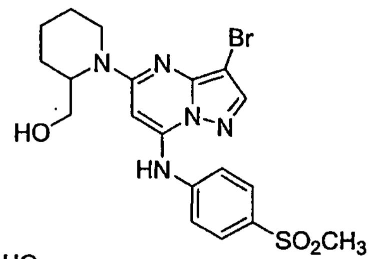













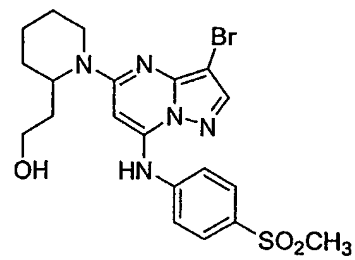

















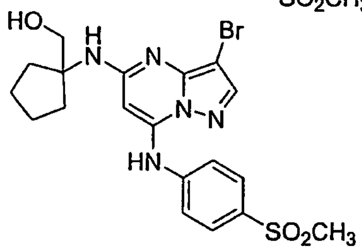



















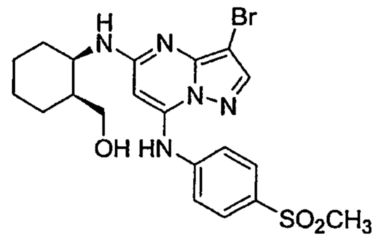



















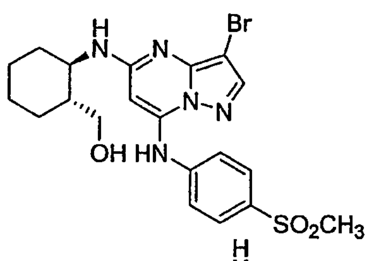

















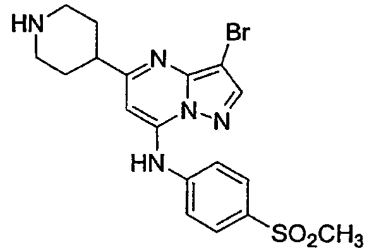


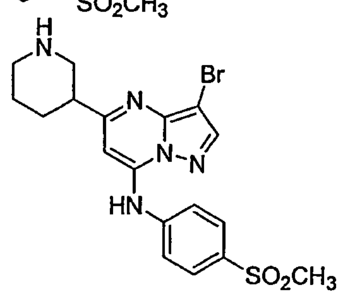












As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched.

The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be

optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

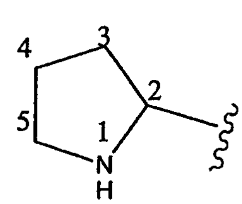
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl,

aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$- and $Y_1Y_2NSO_2$-, wherein Y_1 and Y_2 may be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example; as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protected moieties are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and the like.

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula III, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula III or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting

examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula III can form salts which are also within the scope of this invention. Reference to a compound of Formula III herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula III may be formed, for example, by reacting a compound of Formula III with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington,

D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula III, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to

the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula III can be inhibitors of protein kinases such as the cyclin dependent kinases (CDKs), for example, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 and CDK8. The novel compounds of Formula III are expected to be useful in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974 cited earlier, the disclosure of which is incorporated herein.

More specifically, the compounds of Formula III can be useful in the treatment of a variety of cancers, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of CDKs in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in

the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of Formula III may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that CDK5 is involved in the phosphorylation of tau protein (*J. Biochem,* (1995) 117, 741-749).

Compounds of Formula III may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of Formula III, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpevirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formula III, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human

papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formula III may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of Formula III may also be useful in inhibiting tumor angiogenesis and metastasis.

Compounds of Formula III may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf 1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

Another aspect of this invention is a method of treating a mammal (*e.g.*, human) having a disease or condition associated with the CDKs by administering a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound to the mammal.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula III. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more of anti-cancer treatments such as radiation therapy, and/or one or more anti-cancer agents selected from the group consisting of cytostatic agents, cytotoxic agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin)); taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11), camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methoxtrexate); alkylating agents (such as temozolomide (TEMODAR™ from Schering-Plough Corporation,

Kenilworth, New Jersey), cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASAR™(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl-]-1-piperidinyl]-2-oxoehtyl]-1-piperidinecarboxamide, or SCH 66336 from Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); signal transduction inhibitors (such as, Iressa (from Astra Zeneca Pharmaceuticals, England), Tarceva (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC™ (C-abl kinase inhibitor from Novartis Pharmaceuticals, East Hanover, New Jersey); interferons such as, for example, intron (from Schering-Plough Corporation), Peg-Intron (from Schering-Plough Corporation); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, cytoxan, and gemcitabine.

Other anti-cancer (also known as anti-neoplastic) agents include but are not limited to Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaeuticals, France), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. For example, the CDC2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Compounds of Formula III may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of Formula III may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

Accordingly, in an aspect, this invention includes combinations comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate thereof, and an amount of one or more anti-cancer treatments and anti-cancer agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and at least one pharmaceutically acceptable carrier.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are

known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18^{th} Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this invention is a kit comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one anticancer therapy and/or anti-cancer agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95%

CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. The retention time and observed parent ion are given.

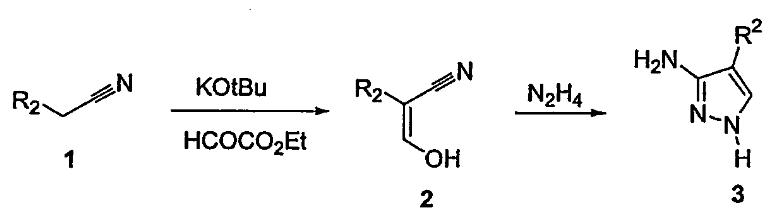
The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Thin layer chromatography: TLC
dichloromethane: CH_2Cl_2
ethyl acetate: AcOEt or EtOAc
methanol: MeOH
trifluoroacetate: TFA
triethylamine: Et_3N or TEA
butoxycarbonyl: n-Boc or Boc
nuclear magnetic resonance spectroscopy: NMR
liquid chromatography mass spectrometry: LCMS
high resolution mass spectrometry: HRMS
milliliters: mL
millimoles: mmol
microliters: μl
grams: g
milligrams: mg
room temperature or rt (ambient): about 25°C.

EXAMPLES

In general, the compounds described in this invention can be prepared through the general routes described below. Treatment of the starting nitrile (Scheme 1) with potassium t-butoxide and ethyl formate gives rise to the

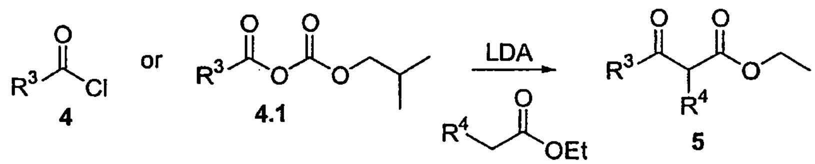
SCHEME 1



intermediate enol 2 which upon treatment with hydrazine gives the desired substituted 3-aminopyrazole. Condensation of the compounds of type 3 with the

appropriately functionalized keto ester of type 5 gives rise to the pyridones 6 as shown in Scheme 3. The keto esters used in this general route are either commercially available or can be made as illustrated in Scheme 2.

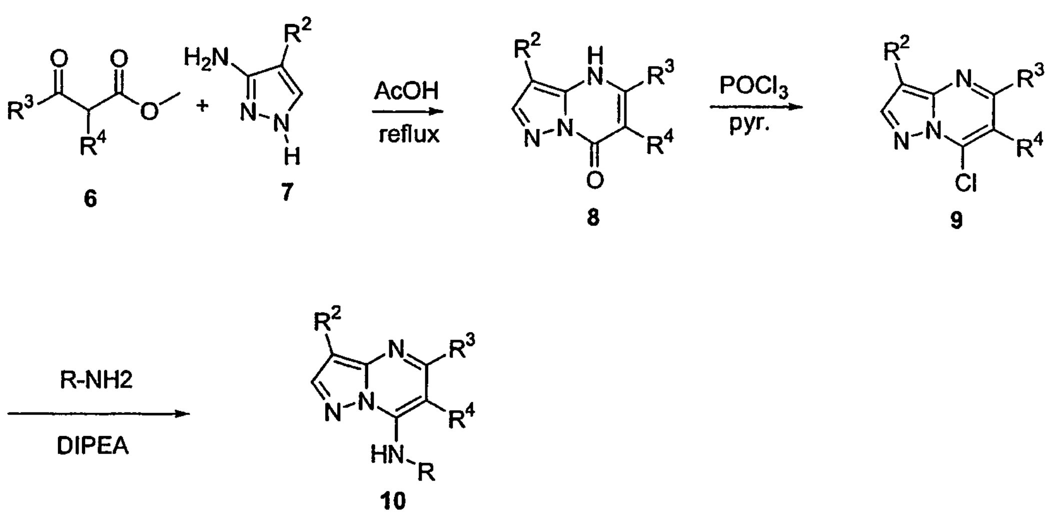
SCHEME 2



The chlorides of type 9 can be prepared by treatment of the pyridones 8 with $POCl_3$. When R^2 is equal to H, substitution in this position is possible on the compounds of type 9 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

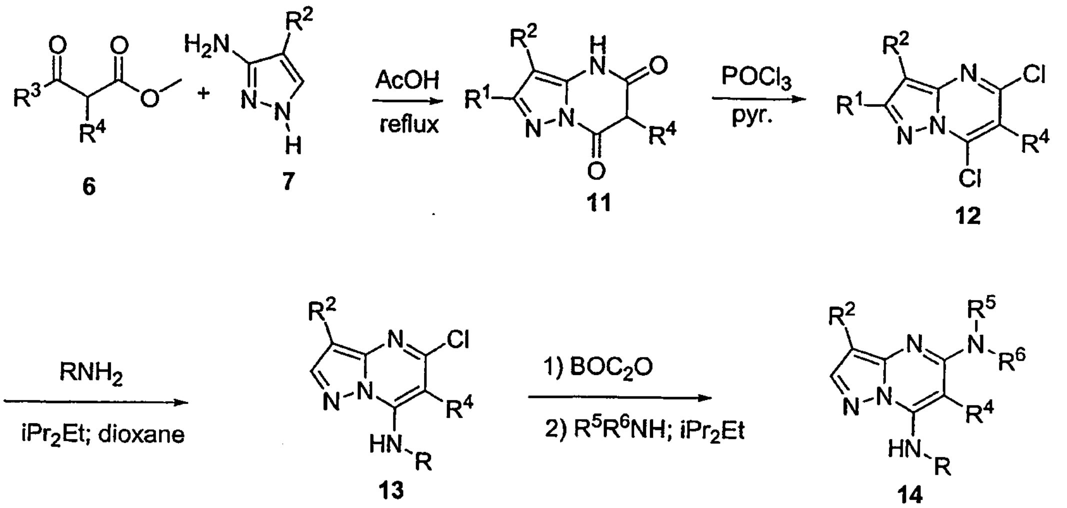
Incorporation of the N7-amino functionality can be accomplished through displacement of the chloride of compounds of type 9 by reaction with the appropriate amine as shown in Scheme 3.

SCHEME 3



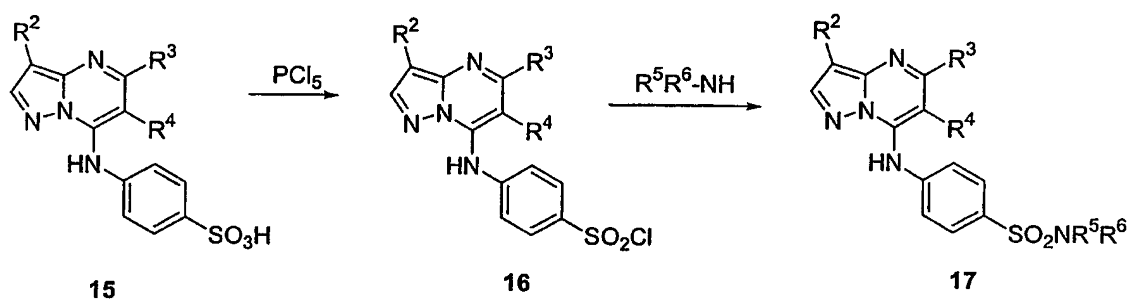
When R^3 = OEt in compounds of type 6, the dichlorides of type 12 can easily be prepared as outlined in Scheme 4. Selective displacements of the 7-chloride gives rise to compounds of type 13, which can readily be converted to products of type 14.

SCHEME 4

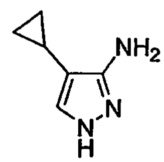


In compounds of type 15 as shown in Scheme 5, chlorination of the sulfonic acid to give 16, followed by direct amine displacement leads to compounds of type 17.

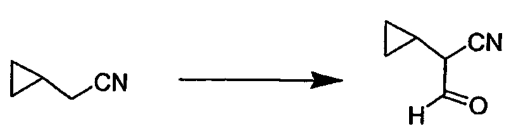
SCHEME 5



PREPARATIVE EXAMPLE 1



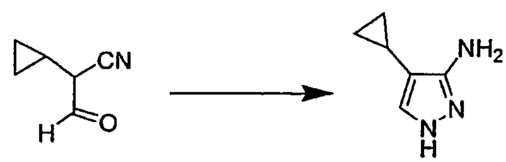
Step A:



A procedure in German patent DE 19834047 A1, p 19 was followed. To a solution of KOtBu (6.17 g, 0.055 mol) in anhydrous THF (40 mL) was added,

dropwise, a solution of cyclopropylacetonitrile (2.0 g, 0.025 mol) and ethyl formate (4.07 g, 0.055 mol) in anhydrous THF (4 mL). A precipitate formed immediately. Stir this mixture for 12 hr. Concentrate under vacuum and stir the residue with Et_2O (50 mL). Decant and wash the resulting residue Et_2O (2 x 50 mL) and remove Et_2O from the residue under vacuum. Dissolve the residue in cold H_2O (20 mL) and adjust to pH 4 – 5 with 12 N HCl. Extract the mixture with CH_2Cl_2 (2 x 50 mL). Combine the organic layers, dry over $MgSO_4$ and concentrate under vacuum to give the aldehyde as a tan liquid.

Step B:

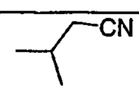
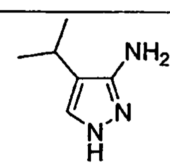


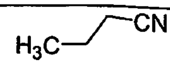
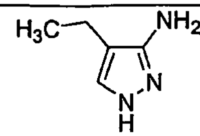
The product from Preparative Example 1, Step A (2.12 g, 0.0195 mol), $NH_2NH_2 \cdot H_2O$ (1.95 g, 0.039 mol) and 1.8 g (0.029 mole) of glacial CH_3CO_2H (1.8 g, 0.029 mol) were dissolved in EtOH (10 mL). It was refluxed for 6 hr and concentrated under vacuum. The residue was slurried in CH_2Cl_2 (150 mL) and the pH adjusted to 9 with 1N NaOH. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the product as a waxy orange solid.

PREPARATIVE EXAMPLES 2-3

By essentially the same procedure set forth in Preparative Example 1, only substituting the nitrile shown in Column 2 of Table 2, the compounds in Column 3 of Table 2 were prepared:

TABLE 2

Prep. Ex.	Column 2	Column 3
2		

3		

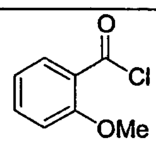
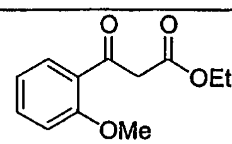
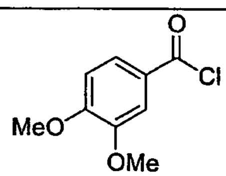
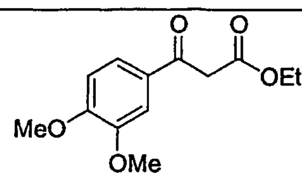
PREPARATIVE EXAMPLE 4

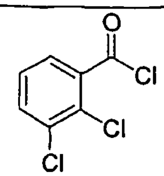
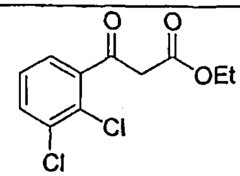
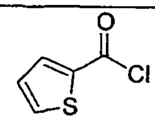
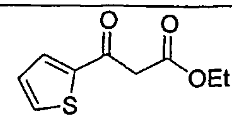
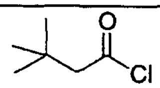
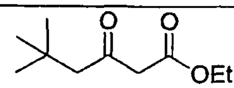
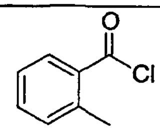
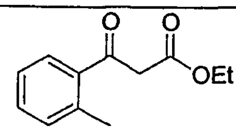
The reactions were done as outlined in (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536.). Thus, to a stirred solution of lithium diisopropylamide in THF at -65 to –70°C was added freshly distilled ethyl acetate, dropwise. The resulting solution was stirred for 30 min and the acid chloride was added as a solution in THF. The reaction mixture was stirred at –65 to –70°C for 30 min and then terminated by the addition of 1 N HCl solution. The resulting two-phased mixture was allowed to warm to ambient temperature. The resulting mixture was diluted with EtOAc (100 mL) the organic layer was collected. The aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude β-keto esters, which were used in the subsequent condensations.

PREPARATIVE EXAMPLES 5-10

By essentially the same procedure set forth in Preparative Example 4 only substituting the acid chlorides shown in Column 2 of Table 3, the *β*-keto esters shown in Column 3 of Table 3 were prepared:

TABLE 3

Prep. Ex.	Column 2	Column 3	DATA
5			Yield = 99% LCMS: MH^+ = 223
6			Yield = 99% LCMS: MH^+ = 253

7			Yield = 80% LCMS: MH^+ = 261
8			Yield = 93% MH^+ = 199
9			Yield=93%
10			Yield=100%

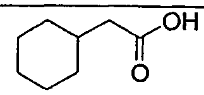
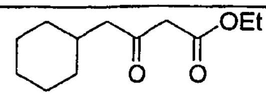
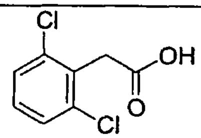
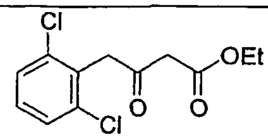
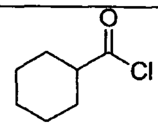
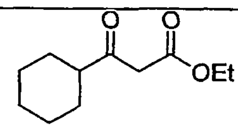
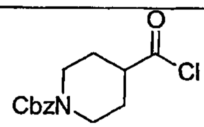
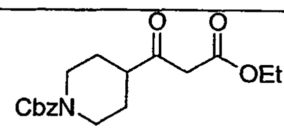
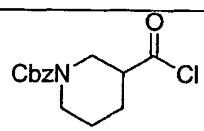
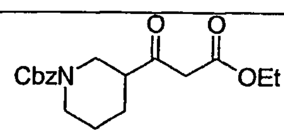
PREPARATIVE EXAMPLE 11

To a solution of the acid in THF was added Et_3N, followed by isobutyl chloroformate at –20 to –30°C. After the mixture was stirred for 30 min at –20 to –30°C, triethylamine hydrochloride was filtered off under argon, and the filtrate was added to the LDA-EtOAc reaction mixture (prepared as outlined in Method A) at –65 to –70°C. After addition of 1 N HCl, followed by routine workup of the reaction mixture and evaporation of the solvents, the crude β-keto esters were isolated. The crude material was used in the subsequent condensations.

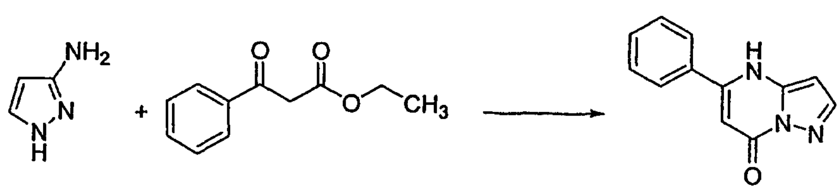
PREPARATIVE EXAMPLES 12 – 13.12

By essentially the same conditions set forth in Preparative Example 11 only substituting the carboxylic acid shown in Column 2 of Table 4, the compounds shown in Column 3 of Table 4 were prepared:

TABLE 4

Prep. Ex.	Column 2	Column 3	DATA
12			Yield = 99% MH^+ = 213
13			Yield = 70% MH^+ = 275
13.10			Yield = 99 MH^+ =199
13.11			Yield = 99 MH^+ = 334
13.12			Yield = 99 MH^+ = 334

PREPARATIVE EXAMPLE 14



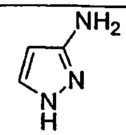
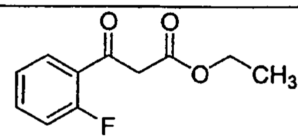
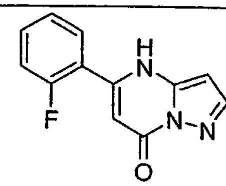
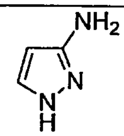
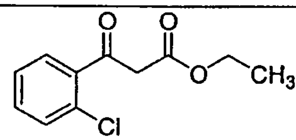
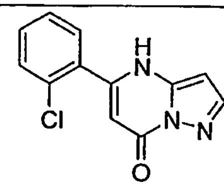
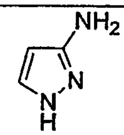
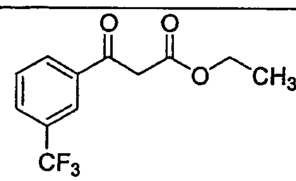
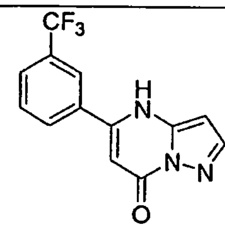
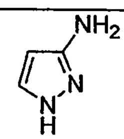
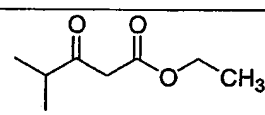
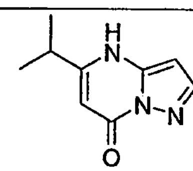
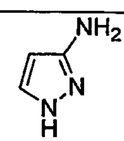
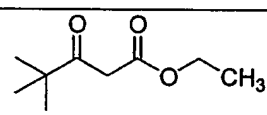
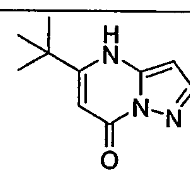
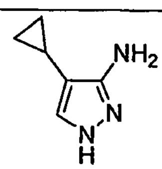
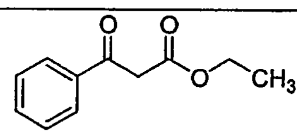
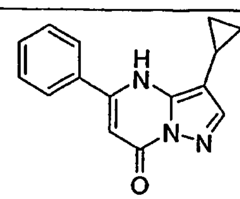
A solution of 3-aminopyrazole (2.0g, 24.07 mmol) and ethyl benzoylacetate (4.58 mL, 1.1 eq.) in AcOH (15 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting solid was diluted with EtOAc and filtered to give a white solid (2.04 g, 40% yield).

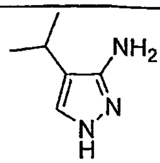
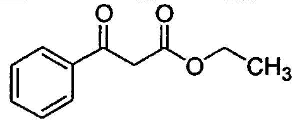
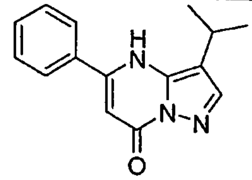
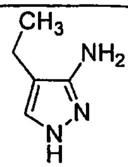
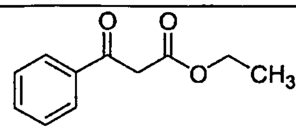
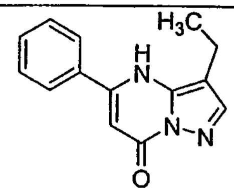
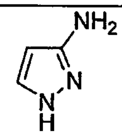
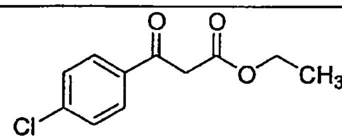
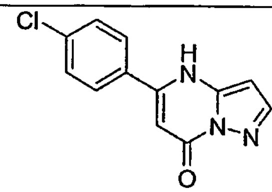
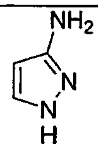
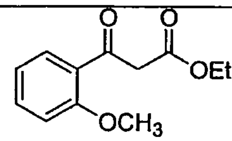
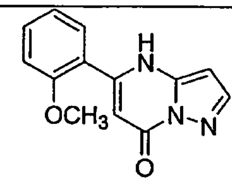
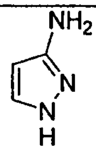
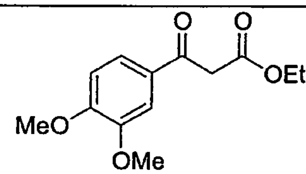
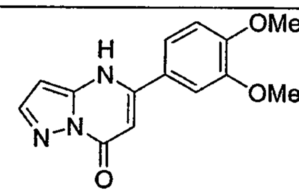
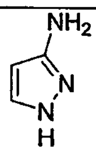
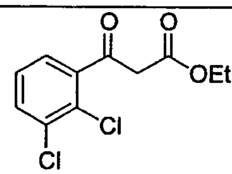
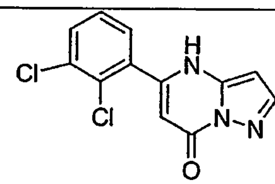
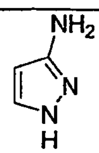
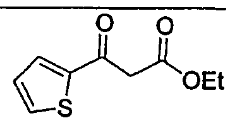
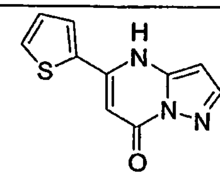
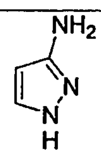
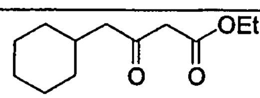
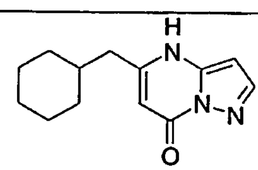
PREPARATIVE EXAMPLES 15-32.15

By essentially the same procedure set forth in Preparative Example 14 only substituting the aminopyrazole shown in Column 2 of Table 5 and the ester shown

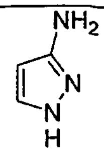
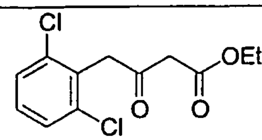
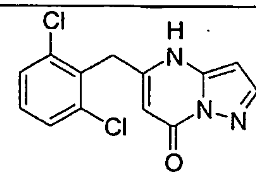
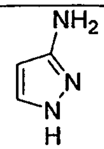
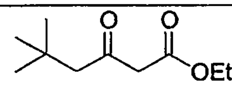
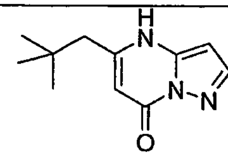
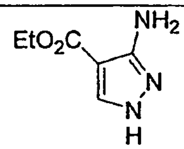
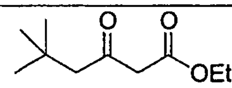
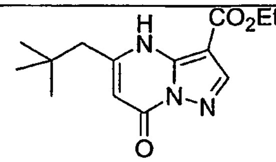
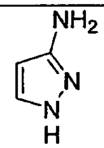
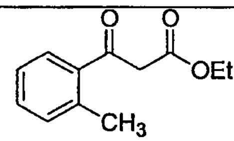
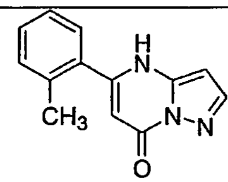
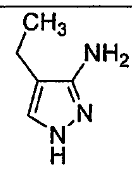
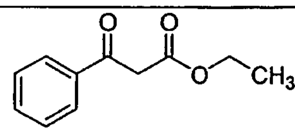
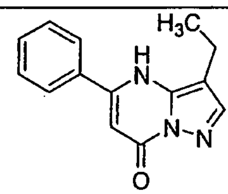
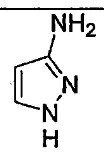
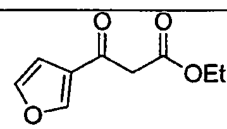
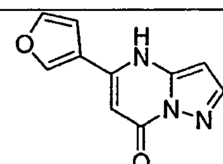
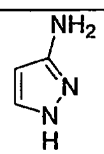
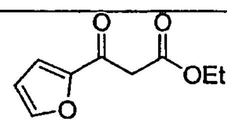
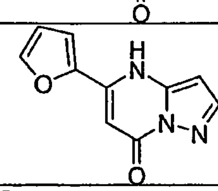
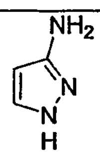
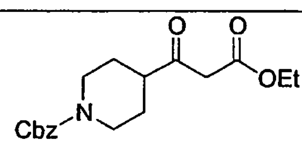
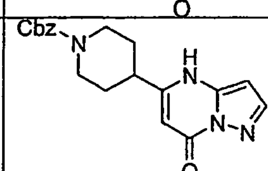
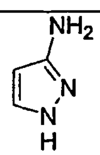
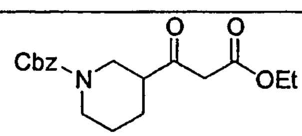
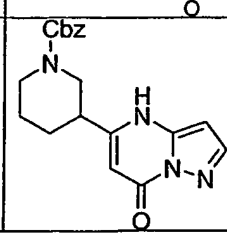
in Column 3 of Table 5, the compounds shown in Column 4 of Table 5 were prepared:

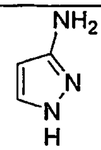
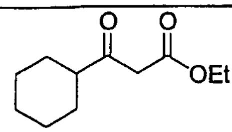
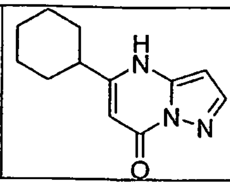
TABLE 5

Prep. Ex.	Column 2	Column 3	Column 4
15			
16			
17			
18			
19			
20			

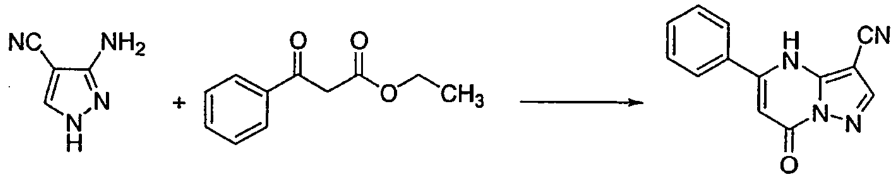
21			
22			
23			
24			
25			
26			
27			
28			

39

29			
30			
31			
32			
32.10			
32.11			
32.12			
32.13			
32.14			

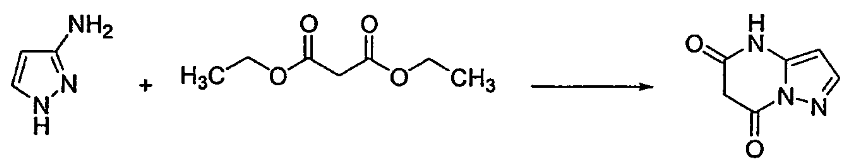
32.15			

PREPARATIVE EXAMPLE 33



Ethyl benzoylacetate (1.76 mL, 1.1 eq.) and 3-amino-4-cyanopyrazole (1.0 g, 9.25 mmol) in AcOH (5.0 mL) and H_2O (10 mL) was heated at reflux 72 hours. The resulting solution was cooled to room temperature, concentrated *in vacuo*, and diluted with EtOAc. The resulting precipitate was filtered, washed with EtOAc, and dried *in vacuo* (0.47 g, 21% yield).

PREPARATIVE EXAMPLE 33.10:

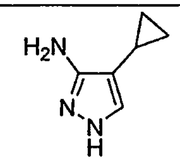
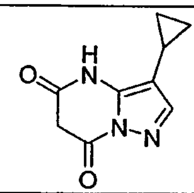
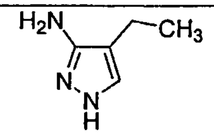
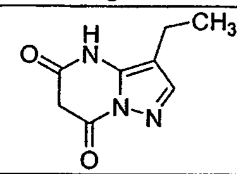


A procedure in US patent 3,907,799 was followed. Sodium (2.3 g, 2 eq.) was added to EtOH (150 mL) portionwise. When the sodium was completely dissolved, 3-aminopyrazole (4.2 g, 0.05 mol) and diethyl malonate (8.7 g, 1.1 eq.) were added and the resulting solution heated to reflux for 3 hours. The resulting suspension was cooled to room temperature and filtered. The filter cake was washed with EtOH (100 mL) and dissolved in water (250 mL). The resulting solution was cooled in an ice bath and the pH adjusted to 1-2 with concentrated HCl. The resulting suspension was filtered, washed with water (100 mL) and dried under vacuum to give a white solid (4.75 g, 63% yield).

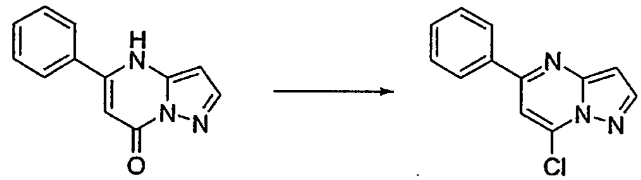
PREPARATIVE EXAMPLES 33.11-33.12:

By essentially the same procedure set forth in Preparative Example 33.10 only substituting the compound shown in Column 2 of Table 5.1, the compounds shown in Column 3 of Table 5.1 are prepared:

TABLE 5.1

Prep. Ex.	Column 2	Column 3
33.11		
33.12		

PREPARATIVE EXAMPLE 34

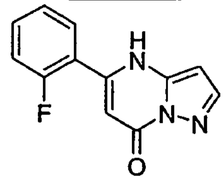
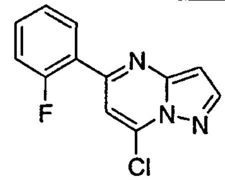
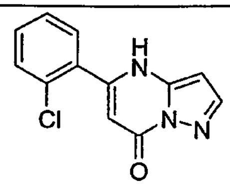
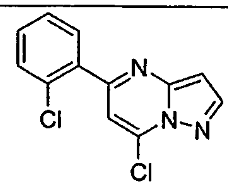
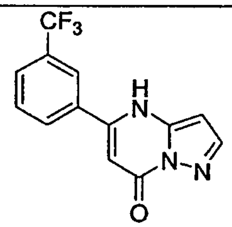
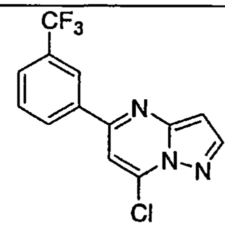
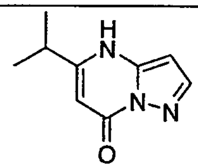
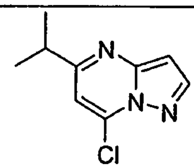
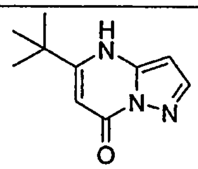
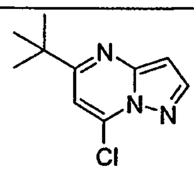
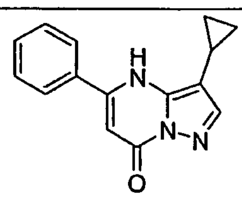
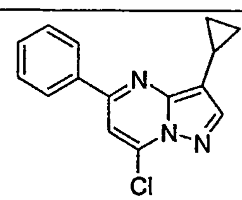
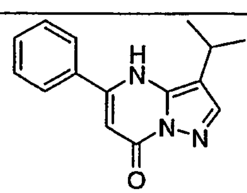
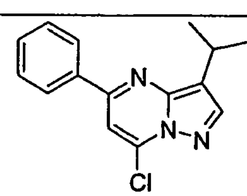


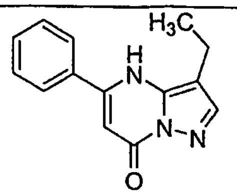
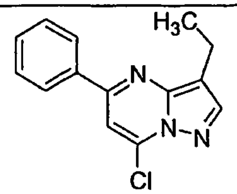
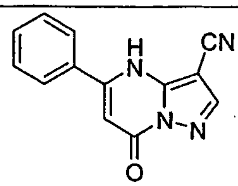
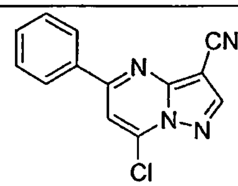
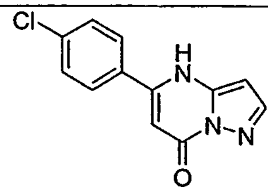
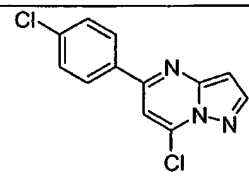
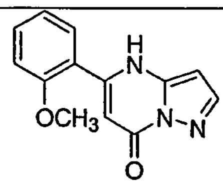
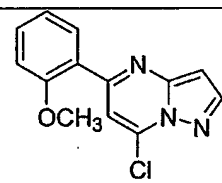
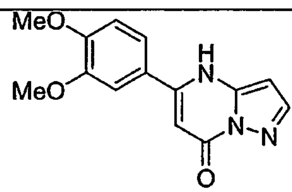
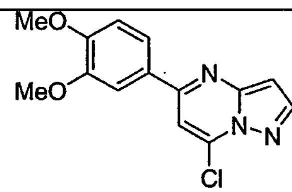
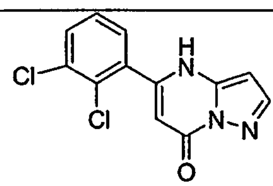
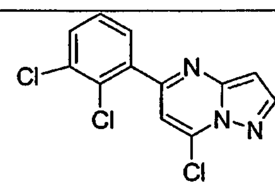
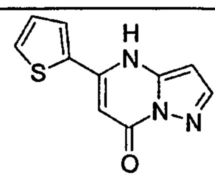
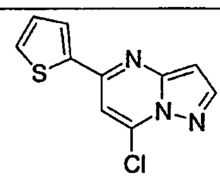
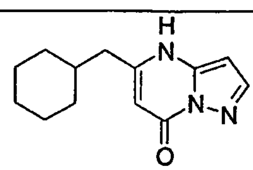
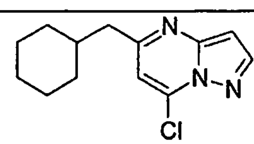
A solution of the compound prepared in Preparative Example 14 (1.0 g, 4.73 mmol) in $POCl_3$ (5 mL) and pyridine (0.25 mL) was stirred at room temperature 3 days. The resulting slurry was diluted with Et_2O, filtered, and the solid residue washed with Et_2O. The combined Et_2O washings were cooled to 0°C and treated with ice. When the vigorous reaction ceased, the resulting mixture was diluted with H_2O, separated, and the aqueous layer extracted with Et_2O. The combined organics were washed with H_2O and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated to give a pale yellow solid (0.86 g, 79% yield). LCMS: MH^+=230.

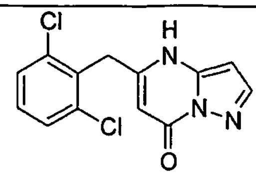
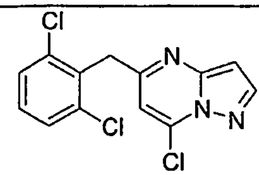
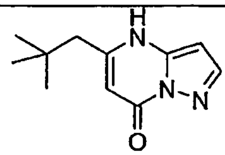
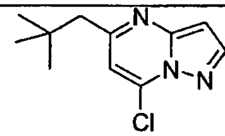
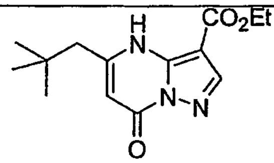
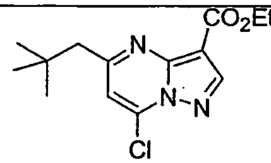
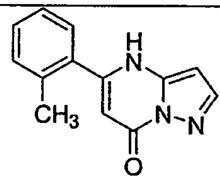
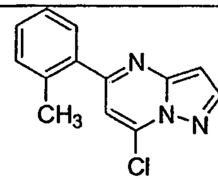
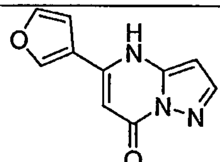
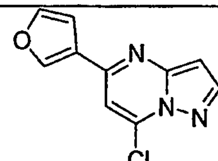
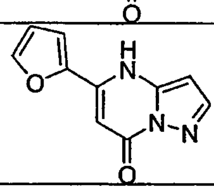
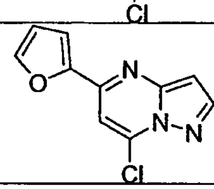
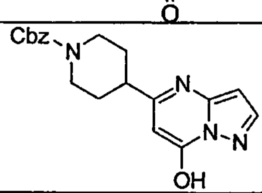
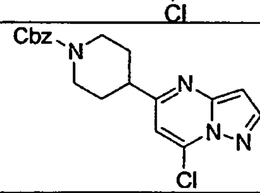
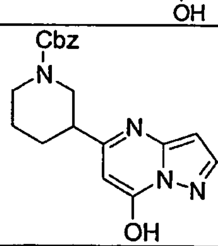
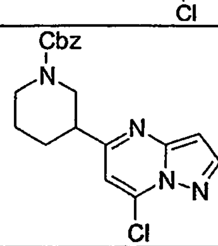
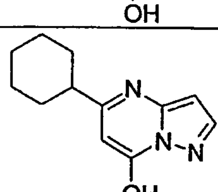
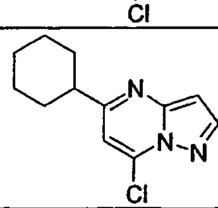
PREPARATIVE EXAMPLE 35-53.14:

By essentially the same procedure set forth in Preparative Example 34, only substituting the compound shown in Column 2 of Table 6, the compounds shown in Column 3 of Table 6 were prepared:

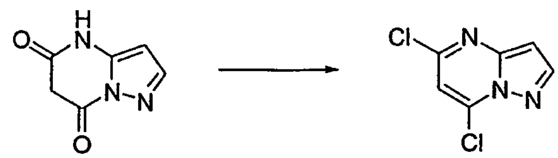
TABLE 6

Prep. Ex.	Column 2	Column 3	DATA
35			LCMS: MH^+=248
36			---
37			LCMS: MH^+=298
38			LCMS: MH^+=196
39			LCMS: MH^+=210
40			---
41			LCMS: MH^+=272

42			---
43			LCMS: MH^+=255
44			---
45			Yield = 65% LCMS: MH^+ = 260
46			Yield = 35% LCMS: MH^+ = 290
47			Yield = 32% LCMS: MH^+ = 298
48			Yield = 45% LCMS: MH^+ = 236
49			Yield = 100% LCMS: MH^+ = 250

50			Yield = 88% LCMS: MH^+ = 314
51			Yield=43% LCMS: MH^+=223
52			Yield=30% LCMS: MH^+=295
53			Yield=98% LCMS: MH^+=244
53.10			
53.11			
53.12			Yield = 96 MH^+ =371
53.13			Yield = 99 MH^+ =371
53.14			Yield = quant. MH^+ =236

PREPARATIVE EXAMPLE 53.15

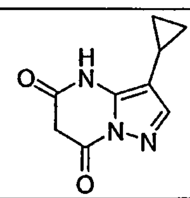
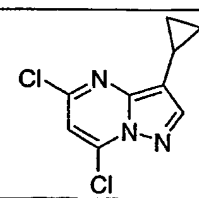
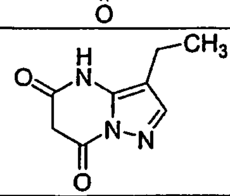
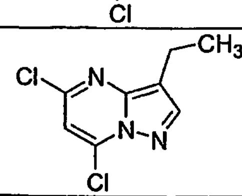


$POCl_3$ (62 mL) was cooled to 5 °C under nitrogen and dimethylaniline (11.4 g, 2.8 eq.) and the compound prepared in Preparative Example 33.10 (4.75 g, 0.032 mol). The reaction mixture was warmed to 60 °C and stirred overnight. The reaction mixture was cooled to 30 °C and the $POCl_3$ was distilled off under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL) and poured onto ice. After stirring 15 minutes, the pH of the mixture was adjusted to 7-8 with solid $NaHCO_3$. The layers were separated and the organic layer was washed with H_2O (3 x 200 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using a 50 : 50 CH_2Cl_2 : hexanes solution as eluent to elute the dimethyl aniline. The eluent was then changed to 75 : 25 CH_2Cl_2 : hexanes to elute the desired product (4.58 g, 77% yield). MS: MH^+=188.

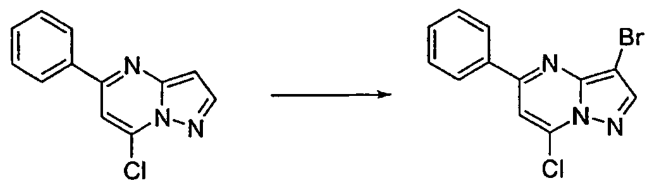
PREPARATIVE EXAMPLES 53.16-53.17

By essentially the same procedure set forth in Preparative Example 53.15 only substituting the compound in Column 2 of Table 6.10, the compounds shown in Column 3 of Table 6.10 are prepared:

TABLE 6.10

Prep. Ex.	Column 2	Column 3
53.16		
53.17		

PREPARATIVE EXAMPLE 54

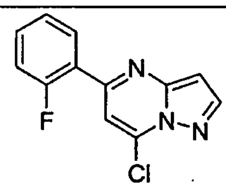
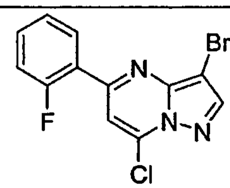
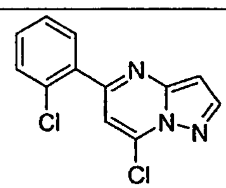
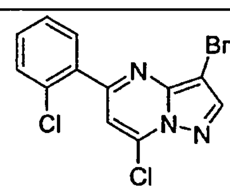
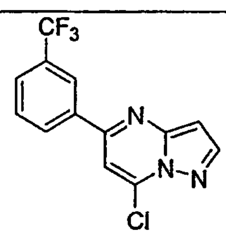
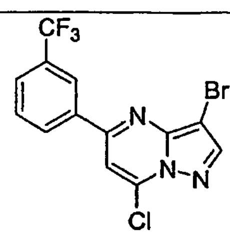


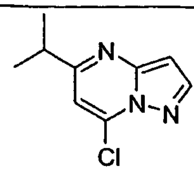
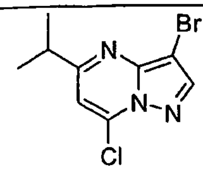
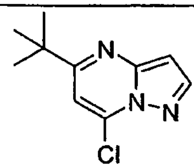
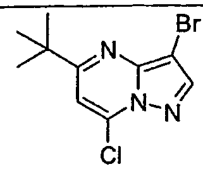
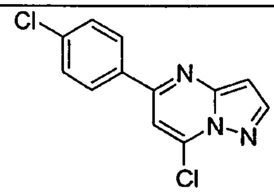
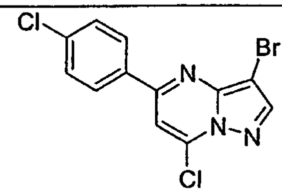
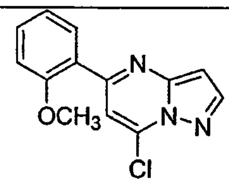
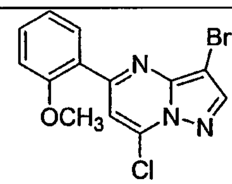
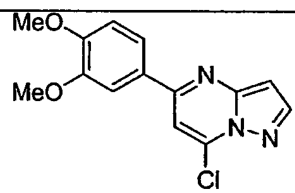
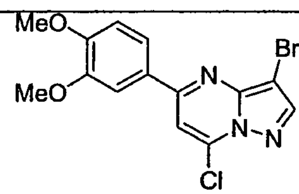
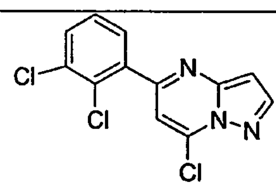
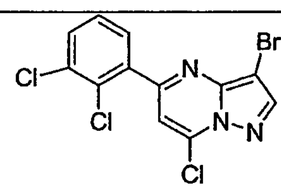
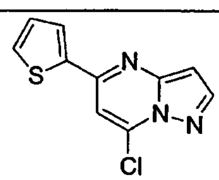
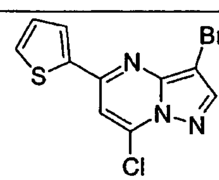
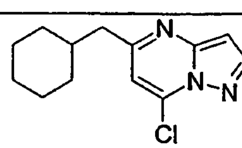
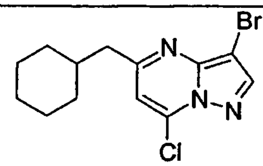
A solution of the compound prepared in Preparative Example 34 (0.10 g, 0.435 mmol) in CH_3CN (3 mL) was treated with NBS (0.085 g, 1.1 eq.). The reaction mixture was stirred at room temperature 1 hour and concentrated under reduced pressure. The crude product was purified by flash chromatography using an 20% EtOAc in hexanes solution as eluent (0.13 g, 100% yield). LCMS: MH^+=308.

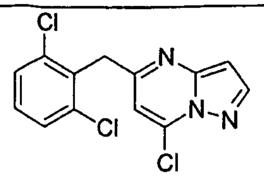
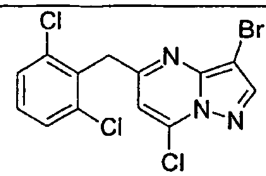
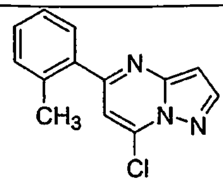
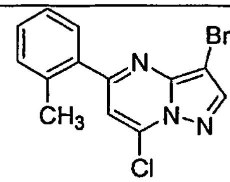
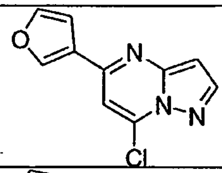
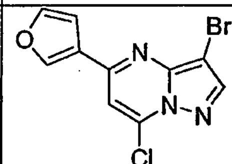
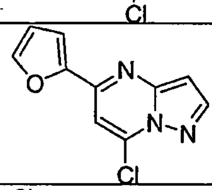
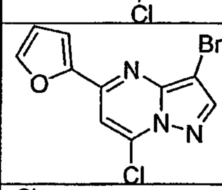
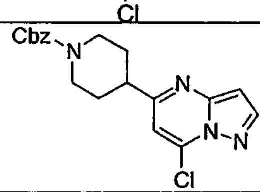
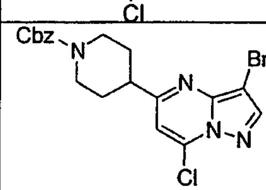
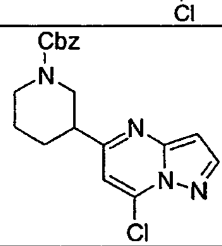
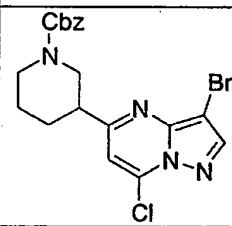
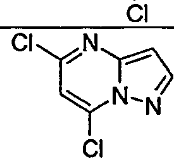
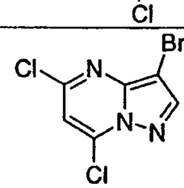
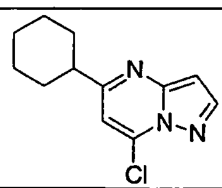
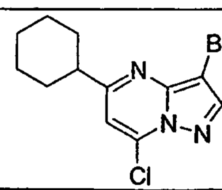
PREPARATIVE EXAMPLES 55-67.15

By essentially the same procedure set forth in Preparative Example 54 only substituting the compounds shown in Column 2 of Table 7, the compounds shown in Column 3 of Table 7 were prepared:

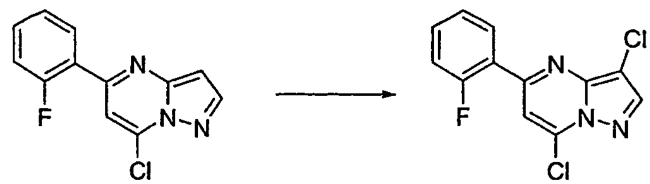
TABLE 7

Prep. Ex.	Column 2	Column 3	CMPD
55			LCMS: MH^+=326
56			LCMS: MH^+=342
57			LCMS: MH^+=376

58			LCMS: MH^+=274
59			LCMS: MH^+=288
60			LCMS: MH^+=342
61			Yield = 75% LCMS: MH^+ = 338
62			Yield = 52% LCMS: MH^+ = 368
63			Yield = 87% LCMS: MH^+ = 376
64			Yield = 100% LCMS: MH^+ = 316
65			Yield = 92% LCMS: MH^+ = 330

66			Yield = 82% LCMS: MH^+ = 395
67			Yield=100% LCMS: MH^+=322
67.10			
67.11			
67.12			Yield = 99 MH^+ =449
67.13			Yield = 95 MH^+ =449
67.14			MH^+=266
67.15			Yield =quant. MH^+ =314

PREPARATIVE EXAMPLE 68:

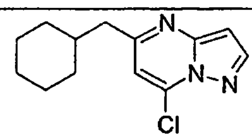
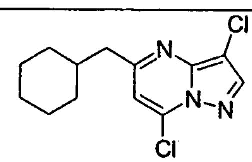


A solution of the compound prepared in Preparative Example 35 (0.3 g, 1.2 mmol) in CH_3CN (15 mL) was treated with NCS (0.18 g, 1.1 eq.) and the resulting solution heated to reflux 4 hours. Additional NCS (0.032 g, 0.2 eq.) added and the resulting solution was stirred at reflux overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue purified by flash chromatography using a 20% EtOAc in hexanes solution as eluent (0.28 g, 83% yield). LCMS: MH^+=282.

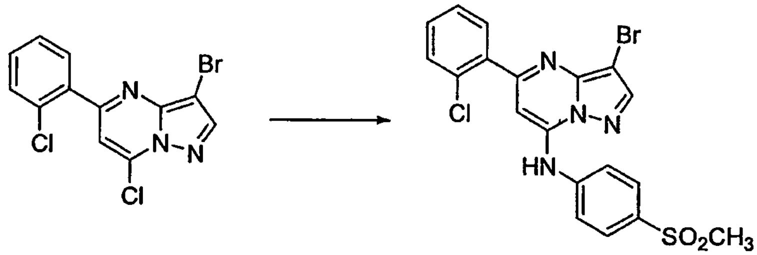
PREPARATIVE EXAMPLE 69:

By essentially the same procedure set forth in Preparative Example 68 only substituting the compound shown in Column 2 of Table 8, the compound shown in Column 3 of Table 7 was prepared:

Table 8

Prep. Ex.	Column 2	Column 3	DATA
69			Yield = 82% LCMS: MH^+ = 286

EXAMPLE 1:



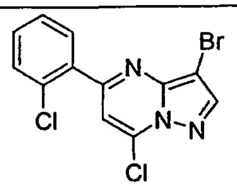
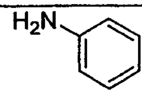
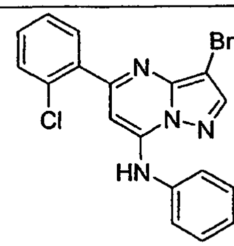
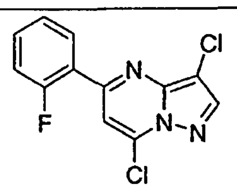
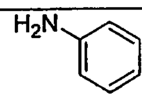
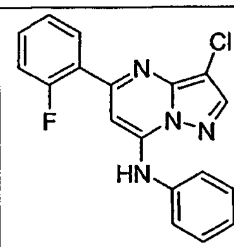
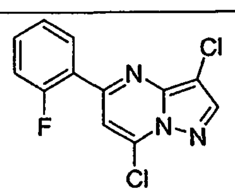
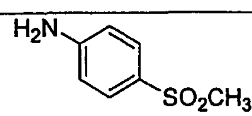
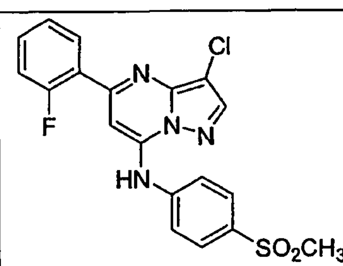
The product from Preparative Example 56 (0.12 g, 0.35 mmol) and 4-methylsulfonylaniline hydrochloride (0.065 g, 0.9 eq) and iPr_2NEt (1.0 mL) were heated to 100°C for 48 hours. The reaction mixture was cooled to room

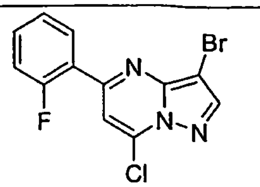
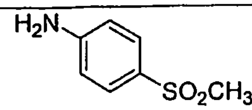
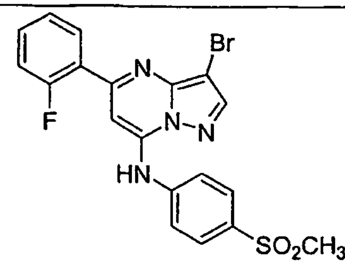
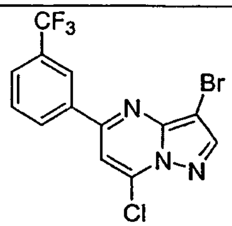
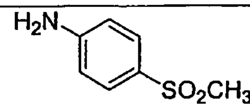
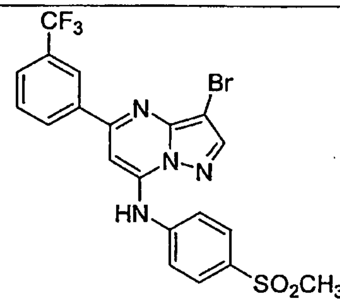
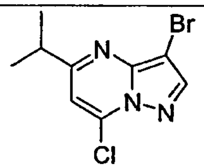
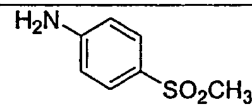
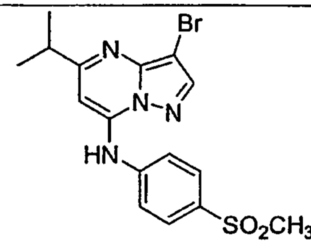
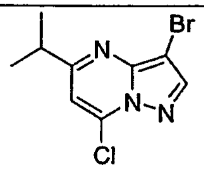
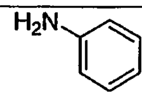
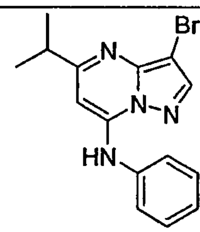
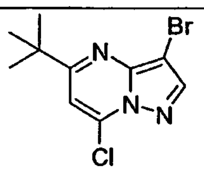
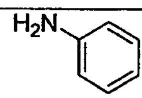
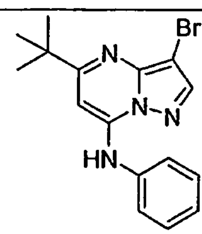
temperature and purified by Preparative thin layer chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.033 g, 23% yield). LCMS: MH^+= 477. mp=180-182°C.

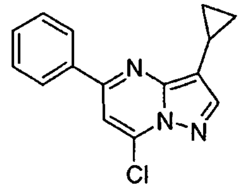
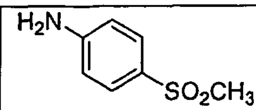
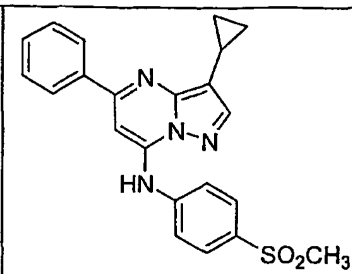
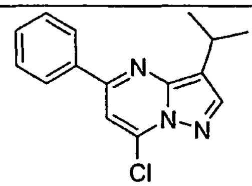
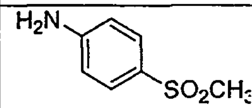
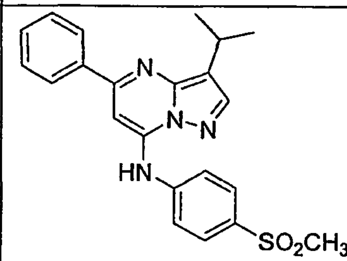
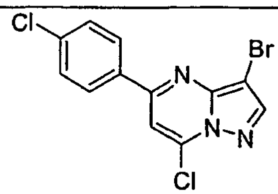
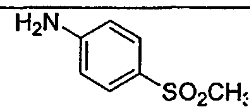
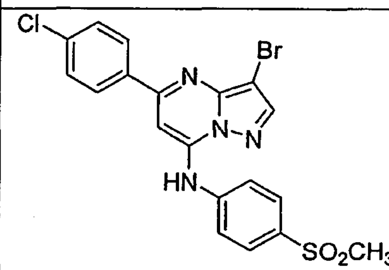
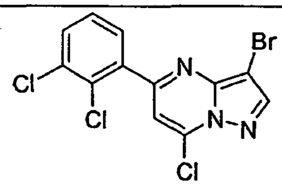
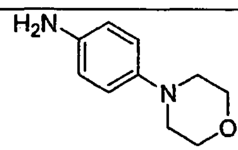
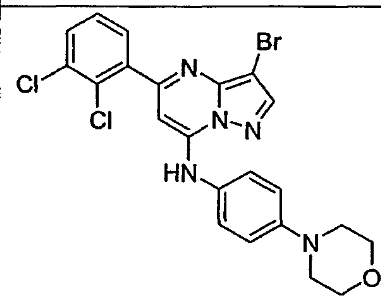
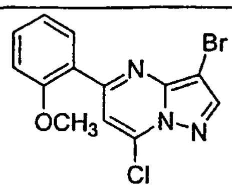
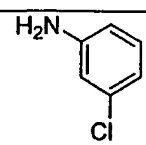
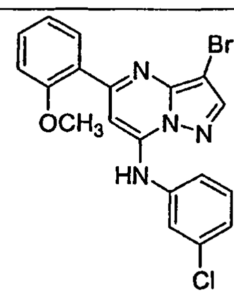
EXAMPLES 2-21.15:

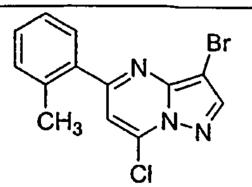
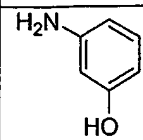
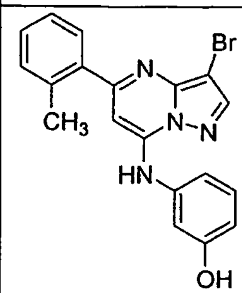
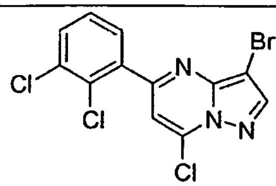
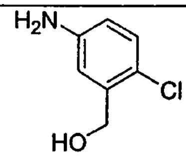
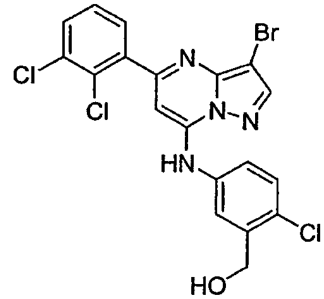
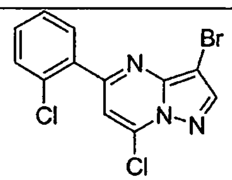
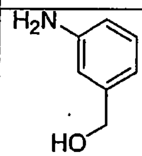
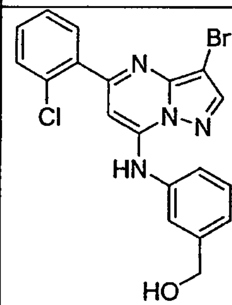
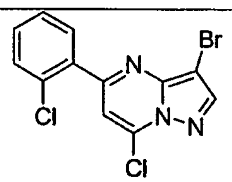
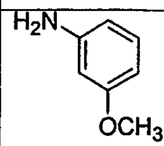
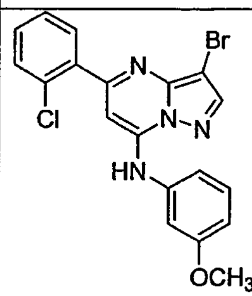
By essentially the same procedure set forth in Example 1 only substituting the compound shown in Column 2 of Table 9 and the amine shown in Column 3 of Table 9, the compounds shown in Column 4 of Table 9 were prepared and are prepared:

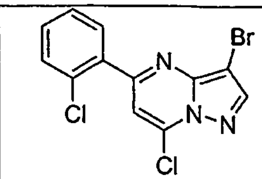
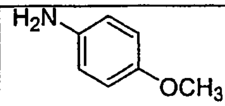
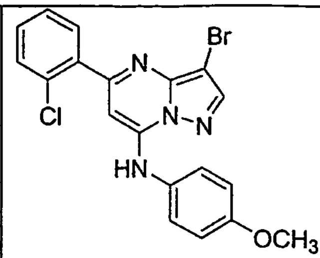
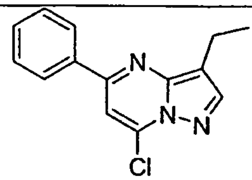
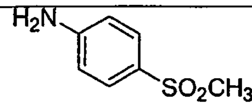
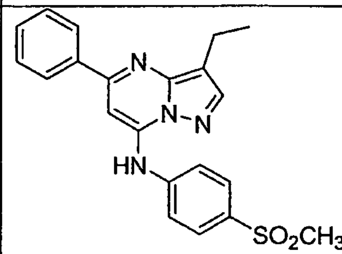
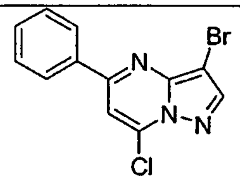
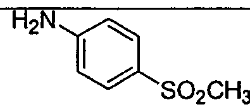
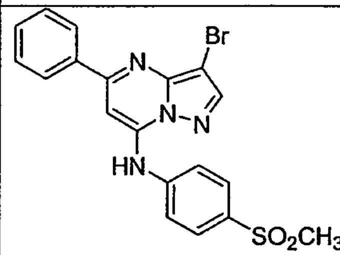
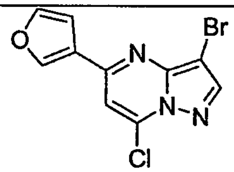
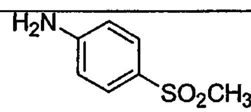
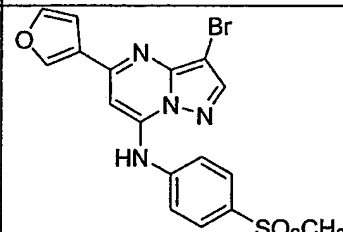
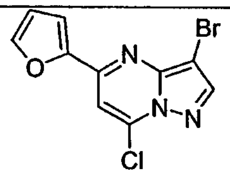
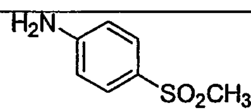
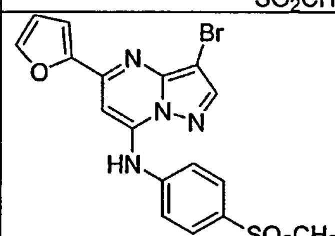
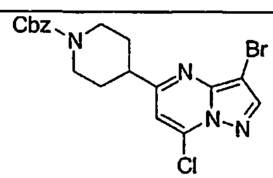
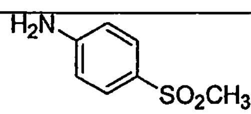
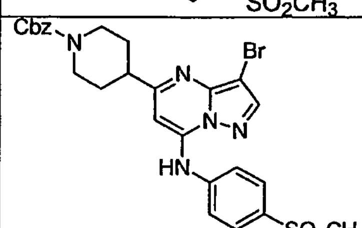
TABLE 9

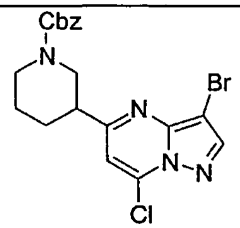
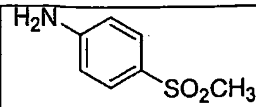
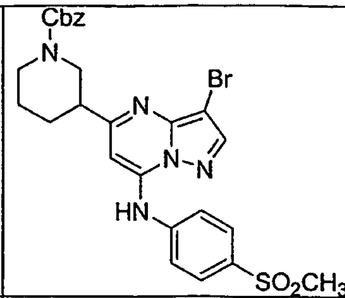
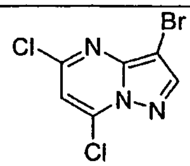
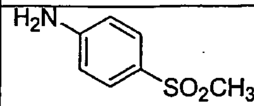
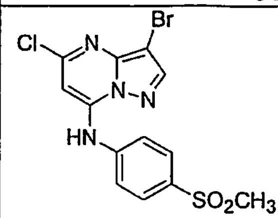
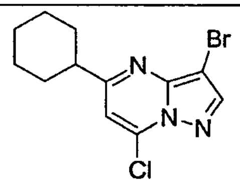
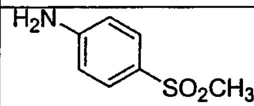
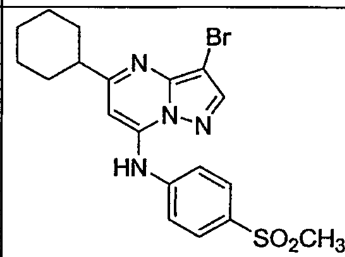
Ex.	Column 2	Column 3	Column 4	DATA
2				LCMS: MH^+= 346; mp= 58-65°C
3				LCMS: MH^+= 339; mp= 112-116°C
4				LCMS: MH^+= 417; mp= 232-235°C

5				LCMS: MH^+= 461; mp= 117-118°C
6				LCMS: MH^+= 511; mp= 210-212°C
7				LCMS: MH^+= 409; mp= 214-215°C
8				LCMS: MH^+= 331; mp= 166-168°C
9				LCMS: MH^+= 345; mp= 144°C

10				LCMS: MH$^+$= 405; mp= 210-211°C
11				LCMS: MH$^+$= 407; mp= 213-216°C
12				LCMS: MH$^+$= 477; mp= 249-253°C
13				**Yield = 72%** LCMS: MH$^+$ = 518.
14				**Yield = 75%** LCMS: MH$^+$ = 429.

15				Yield= 99% LCMS: MH^+= 395
16				**Yield = 45% LCMS: MH^+ = 497.**
17				
18				

19				
20				LCMS: MH^+= 393; mp= 192-194°C
21				LCMS: $M2H^+$= 445; mp= 202-204°C
21.10				
21.11				
21.12				

21. 13				
21. 14				MH^+ = 401
21. 15				

Additional data for select examples is shown below:

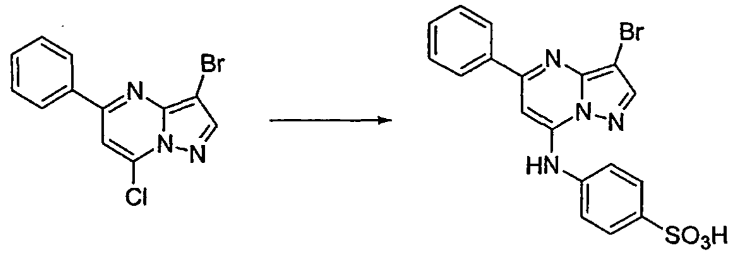
EXAMPLE 13: ^{1}H NMR ($CDCl_3$) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.66-7.64 (m, 2H), 7.60-7.39 (m, 3H), 7.10-7.07 (m, 2H), 6.56 (s, 1H), 3.99 (dd, J = 5.1, 4.5 Hz, 4H), **3.31 (dd, J = 5.1, 4.5 Hz, 4H).**

EXAMPLE 14: ^{1}H NMR ($CDCl_3$) δ 8.16(s, 1H),8.14(d, J=2.1 Hz, 1H), 7.63 (m, 1H),7.5 -7.45 (m,2H), 7.23-7.09(m,3H), 6.84-6.76 (m, 2H),6.64 (m, 1H), 4.03 (s, 3H).

EXAMPLE 15: ^{1}H NMR ($CDCl_3$)δ8.32(s,1H),7.51(d,1H), 7.43-7.33(m, 4H), 6.78(d, 2H),6.72(t, 1H), 2.52(s,3H).

EXAMPLE 16: ^{1}H NMR (CD_3OD) δ 8.31 (s, 1H), 7.75-7.69 (m, 2H),7.64-7.60 (m, 2H),7.56-7.37 (m, 2H),6.37 (s, 1H), 4.79 (s, 2H).

<u>**EXAMPLE 22**</u>

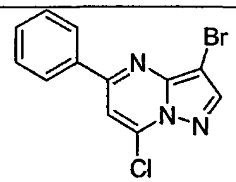
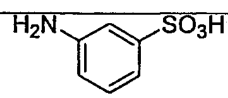
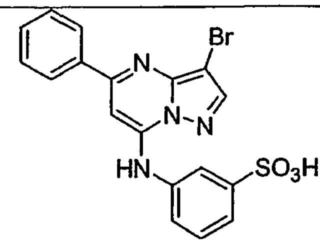
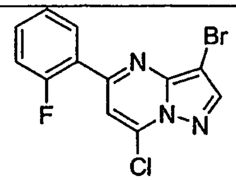
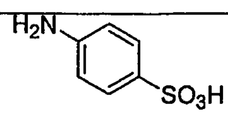
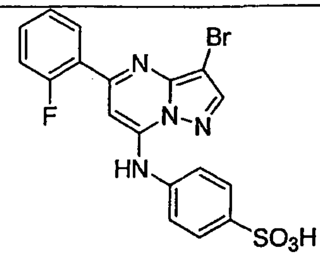


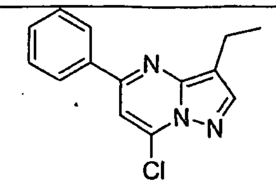
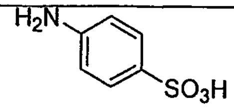
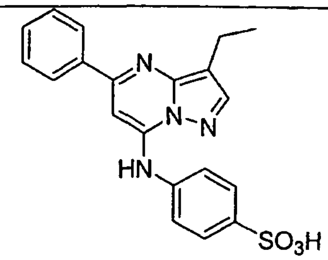
Anhydrous DMF (80 mL) was added under N_2 to a mixture of sulfanilic acid (3.10 g, 17.9 mmol) and NaH (60 % in mineral oil, 1.43 g, 35.8 mmol), the mixture was stirred at 25°C for 2 hr, then the product from Preparative Example 54 (5.00 g, 16.2 mmol) was added. The mixture was stirred at 25°C for 24 hr, the solvent was then evaporated and the residue was purified by chromatography on silica gel using EtOAc:MeOH (4:1) as eluent to yield pale yellow solid (2.32 g, 32% yield). LCMS: MH^+= 447. mp>250°C.

EXAMPLES 23-26

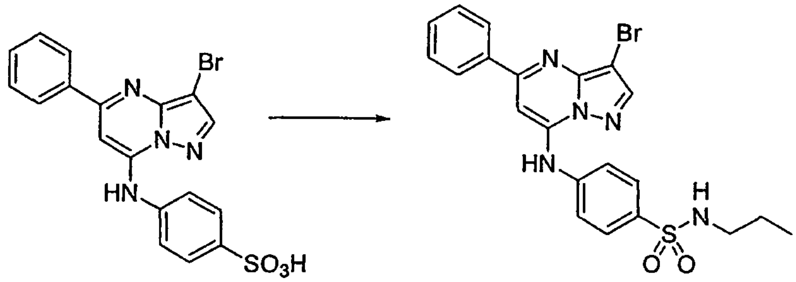
By essentially the same procedure set forth in Example 22 only substituting the compound shown in Column 2 of Table 10 and the amine shown in column 3 of Table 10, the compounds shown in Column 4 of Table 10 were prepared.

TABLE 10

Ex.	Column 2	Column 3	Column 4	DATA
24				LCMS: $M2H^+$= 445; mp= 206-208°C
25				LCMS: $M2H^+$= 465; mp >250° C

26				LCMS: MH^+= 395; mp >250° C

EXAMPLE 27

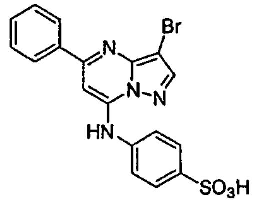
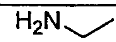
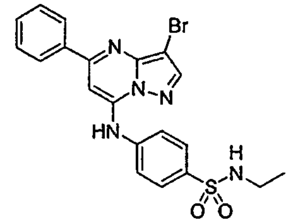
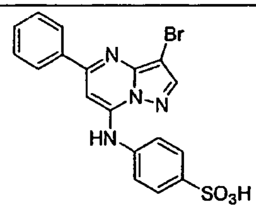
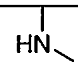
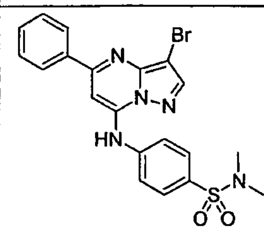
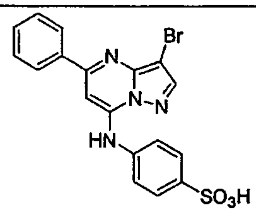
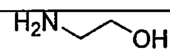
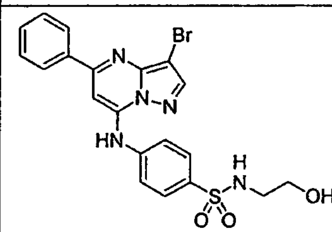
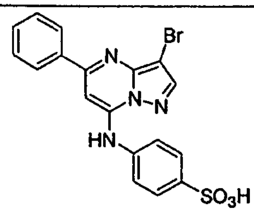
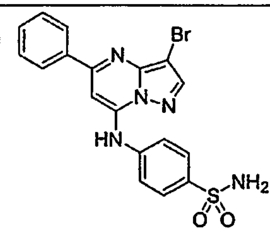
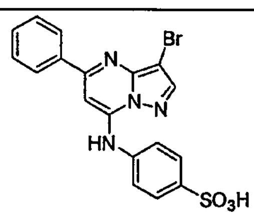
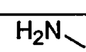
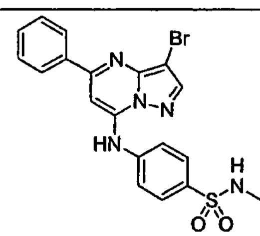


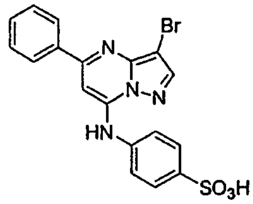
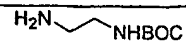
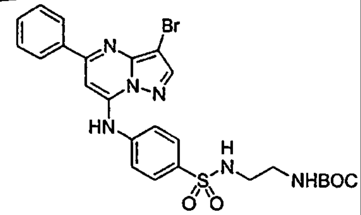
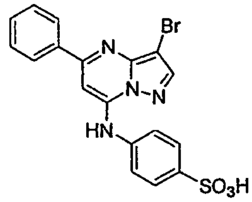
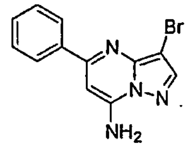
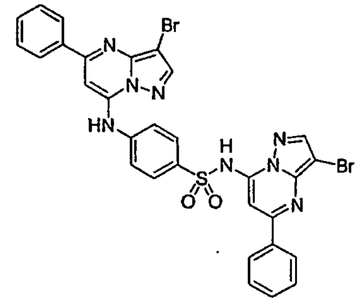
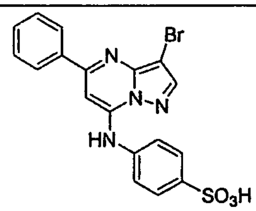
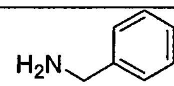
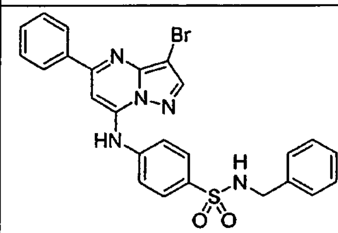
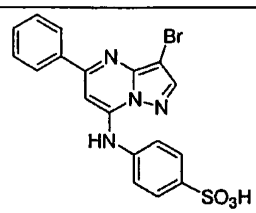
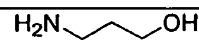
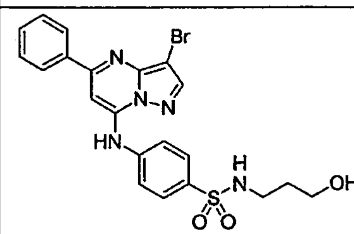
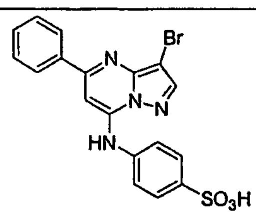
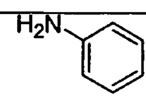
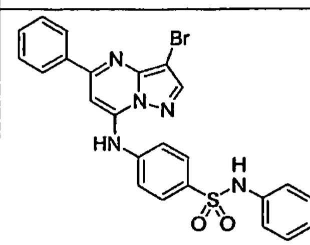
The product from Example 22 (44 mg, 0.10 mmol), and PCl_5 (21 mg, 0.10 mmol) in anhydrous 1,2-dichloroethane were stirred and refluxed under N_2 for 2.5 hr. The mixture was cooled to 25°C, propylamine (0.20 mL, 2.4 mmol) was added, and the mixture was stirred at 25°C for 2 hr. The solvent was then evaporated and the residue was purified by chromatography on silica gel using CH_2Cl_2:EtOAc (20:1) as eluent to yield pale yellow solid (26 mg, 54% yield). LCMS: MH^+= 486. mp=201-203°C.

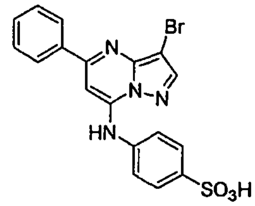
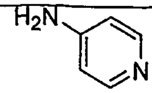
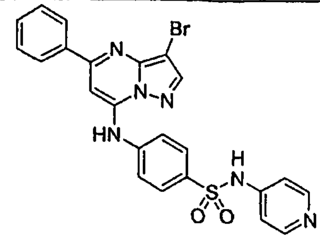
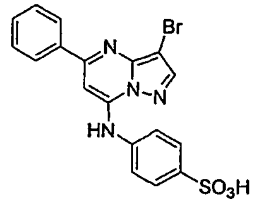
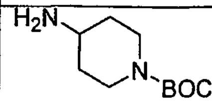
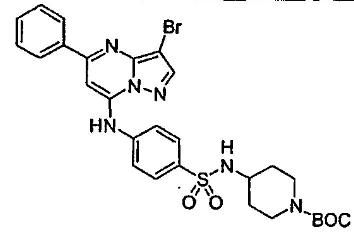
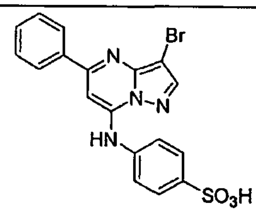
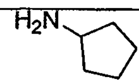
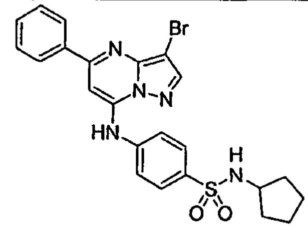
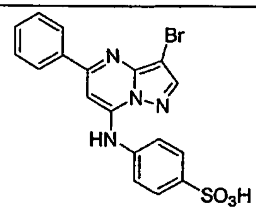
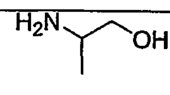
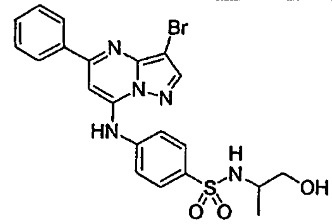
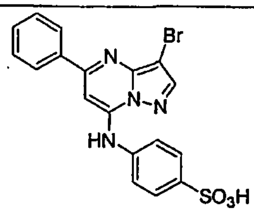
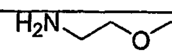
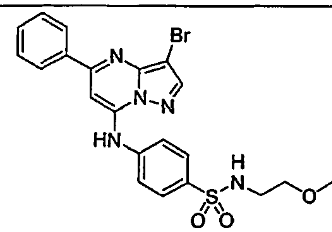
EXAMPLES 28-67

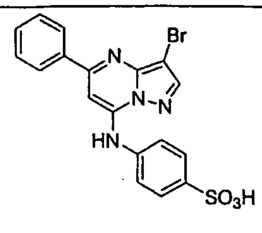
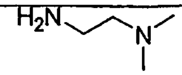
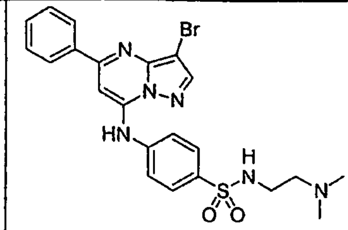
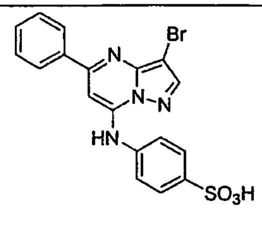
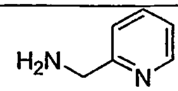
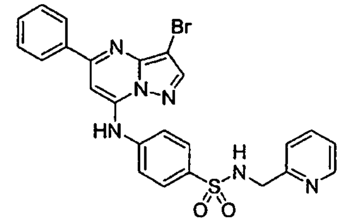
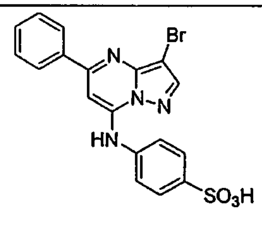
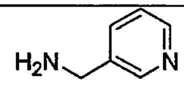
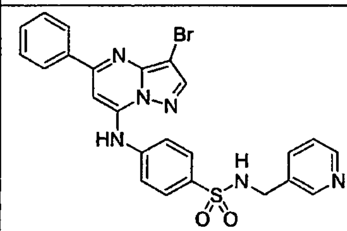
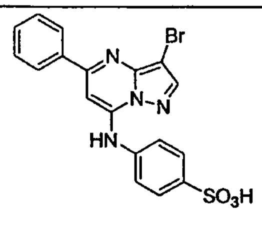
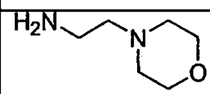
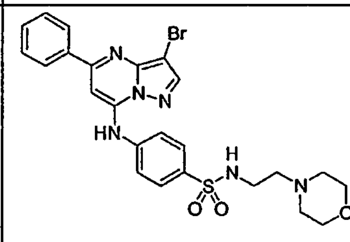
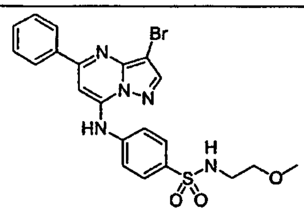
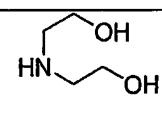
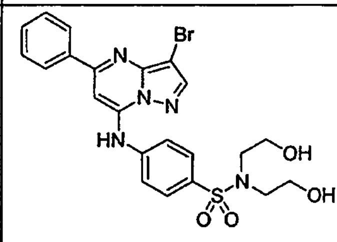
By essentially the same procedure set forth in Example 27 only substituting the compound shown in Column 2 of Table 11 and the amine shown in Column 3 of Table 11, the compounds shown in Column 4 of Table 11 were prepared:

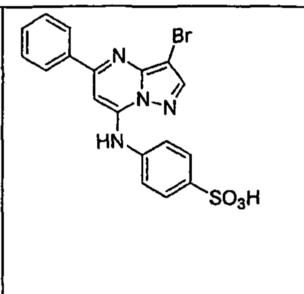
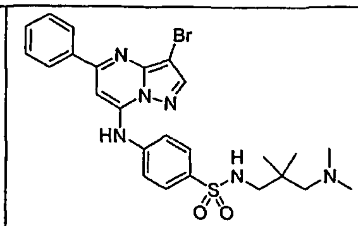
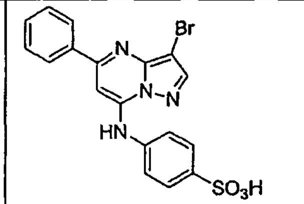
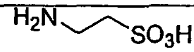
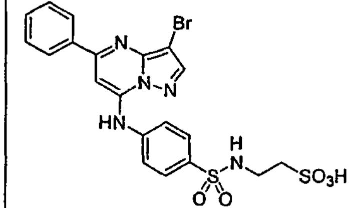
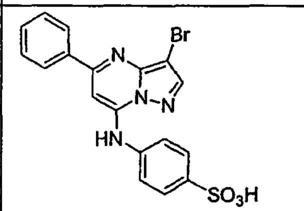
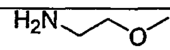
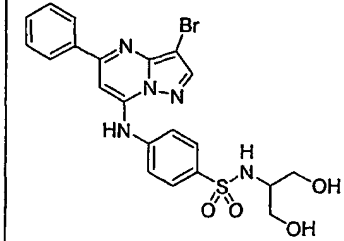
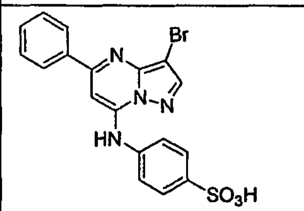
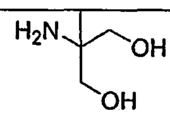
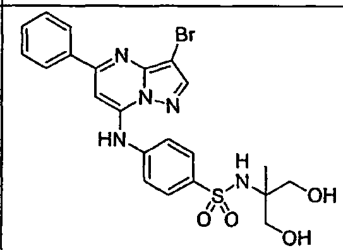
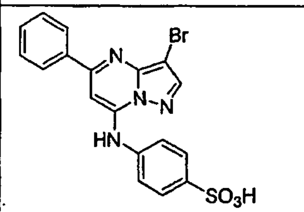
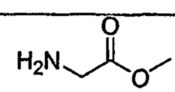
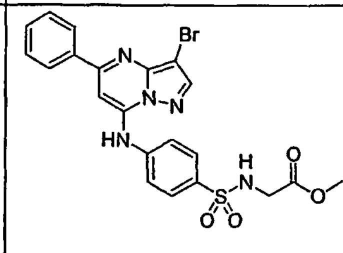
TABLE 11

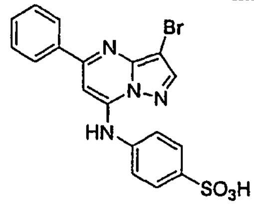
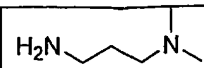
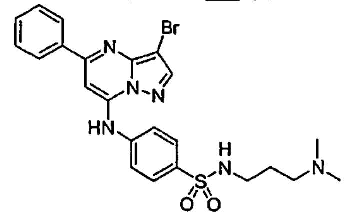
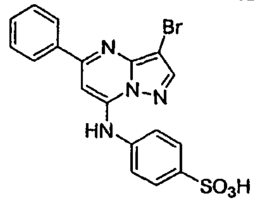
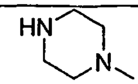
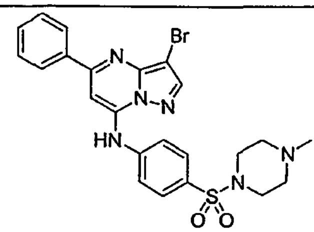
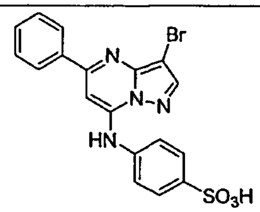
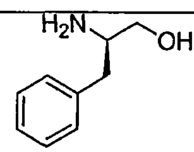
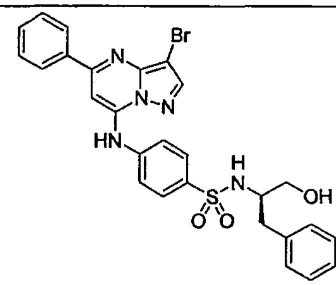
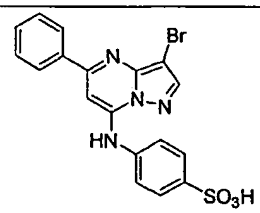
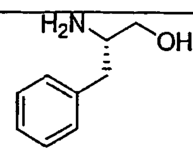
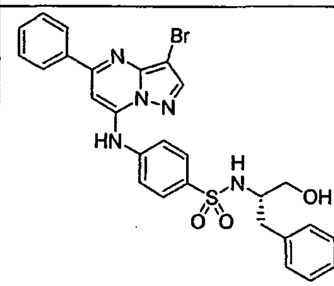
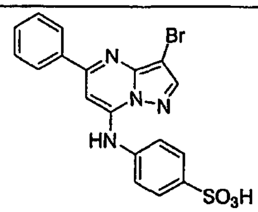
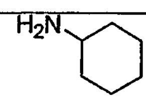
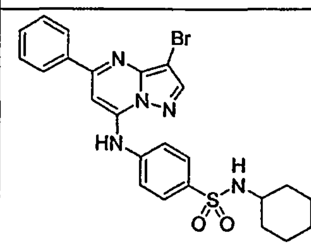
Ex.	Column 2	Column 3	Column 4	DATA
28				LCMS: $M2H^+$= 474; mp= 101-104°C
29				LCMS: $M2H^+$= 472; mp= 237-239°C
30				LCMS: M^+= 488; mp= 175-177°C
31		NH_4OH		LCMS: MH^+= 444; mp= 206-208°C
32				LCMS: MH^+= 458; mp= 231-233°C

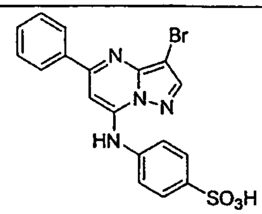
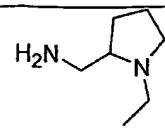
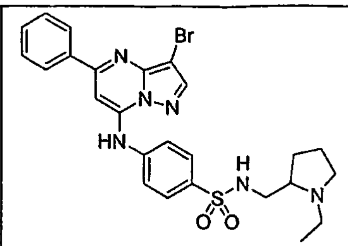
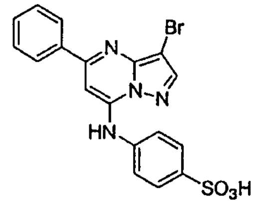
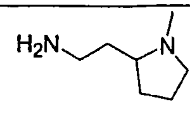
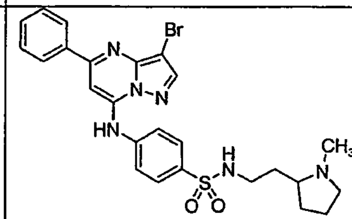
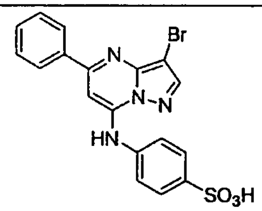
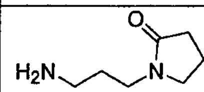
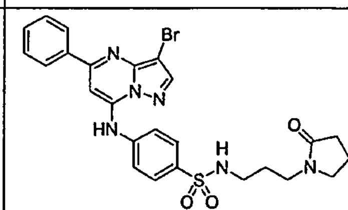
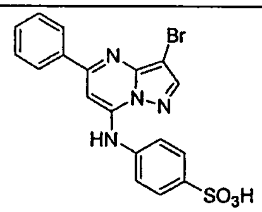
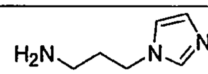
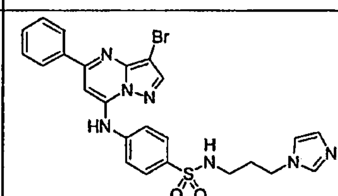
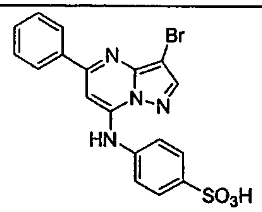
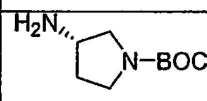
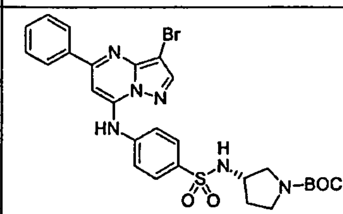
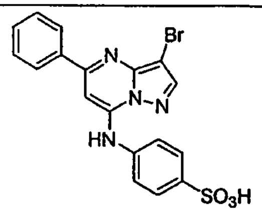
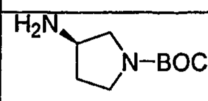
33				LCMS: MH^+= 589; mp= 195-197°C
34				LCMS: MH^+= 717;
35				LCMS: MH^+= 536; mp= 216-218°C
36				LCMS: M^+= 502; mp= 165-168°C
37				LCMS: MH^+= 522; mp= 147-150°C

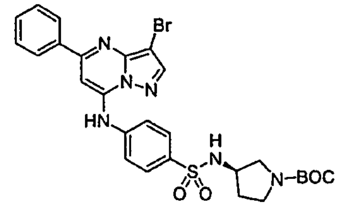
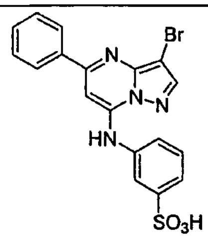
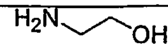
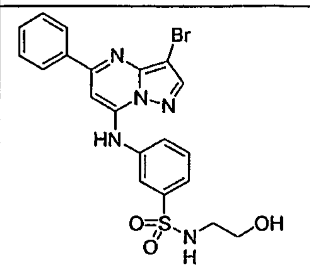
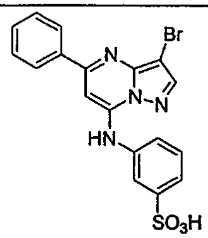
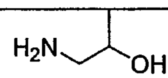
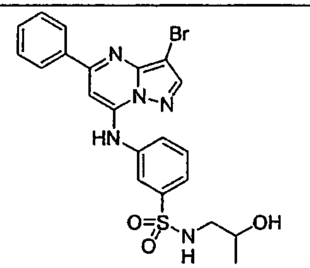
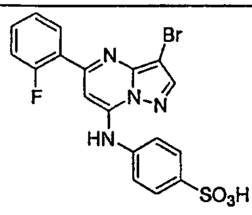
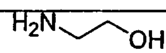
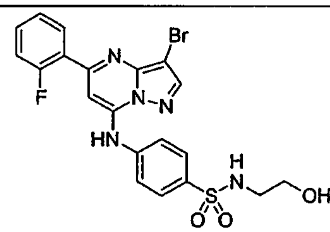
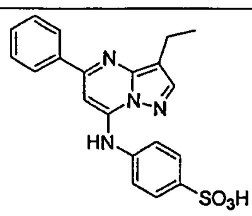
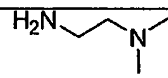
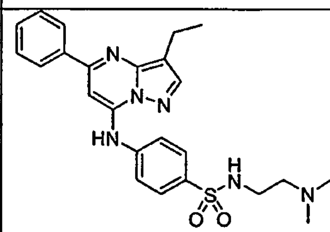
38				LCMS: $M2H^+$= 523; mp= 192-195°C
39				LCMS: MH^+= 629; mp= 127-129°C
40				LCMS: MH^+= 514; mp >200°C (dec.)
41				LCMS: $M2H^+$= 504; mp >200°C (dec.)
42				LCMS: $M2H^+$= 504; mp= 172-173°C

43				LCMS: MH^+= 517; mp= 165-167°C
44				LCMS: $M2H^+$= 537; mp= 101-103°C
45				LCMS: $M2H^+$= 537; mp= 110-114°C
46				LCMS: $M2H^+$= 559; mp=
47				LCMS: M^+= 532; mp= 90-92°C

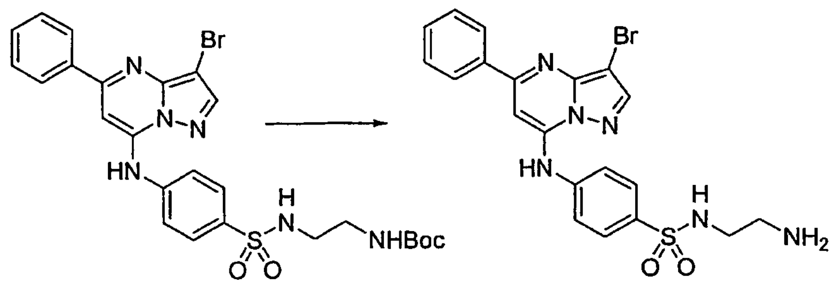
48				LCMS: MH^+= 559; mp= 163-165°C
49				LCMS: M^+= 552; mp= 206-208°C
50				LCMS: MH^+= 520; mp= 122-124°C
51				LCMS: M^+= 532; mp= 98-100°C
52				LCMS: $M2H^+$= 518; mp= 182-184°C

53				LCMS: MH^+= 531; mp= 78-80°C
54				LCMS: MH^+= 529; mp= 228-230°C
55				LCMS: MH^+= 580; mp= 108-110°C
56				LCMS: MH^+= 580; mp= 102-105°C
57				LCMS: $M2H^+$= 528; mp=

58				LCMS: M2H+= 557 m.p.= 204-207
59				LCMS: M2H+= 557
60				LCMS: M2H+= 571 m.p.= 114 -117
61				LCMS: M2H+= 554 m.p.= 127- 130
62				LCMS: M2H+= 613 m.p.= 145 -149
63				LCMS: M2H+= 613 m.p.= 137 -140

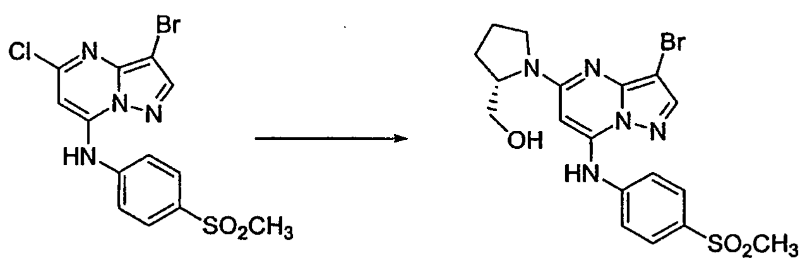
				
64				LCMS: $M2H^+$= 490; mp= 87-90°C
65				LCMS: $M2H^+$= 504; mp= 115-120°C
66				LCMS: $M2H^+$= 508; mp=
67				LCMS: MH^+= 465; mp= 99-101°C

EXAMPLE 68



Trifluoroacetic acid (2.0 mL) was added at 0°C to a solution of the product from Preparative Example 33 (200 mg, 0.34 mmol) in anhydrous CH_2Cl_2. The mixture was stirred at 0°C for 5 min, then at 25°C for 90 min, and then it was poured onto solid Na_2CO_3 (10.0 g). H_2O (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3x25 mL). The extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified by chromatography on silica gel using CH_2Cl_2:MeOH:conc. NH_4OH (10:1:0.1) as eluent to yield pale yellow solid (100 mg, 60% yield). LCMS: M^+= 487. mp=110-112°C.

EXAMPLE 69:

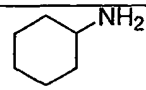
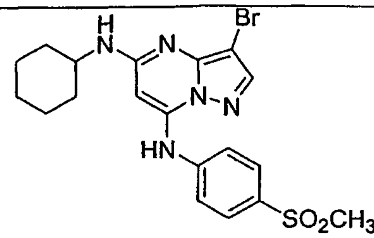
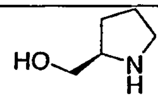
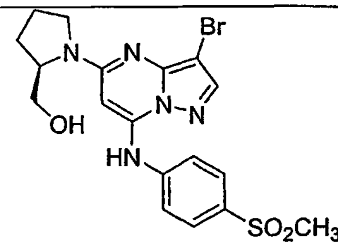
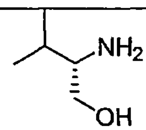
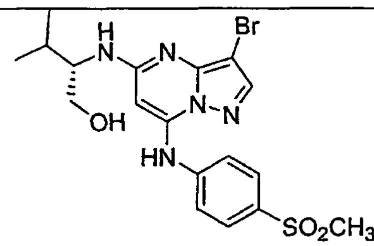
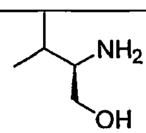
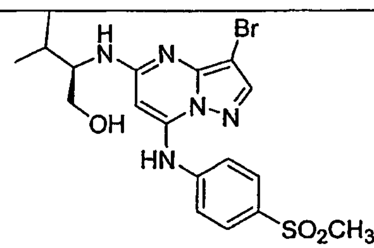
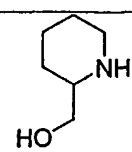
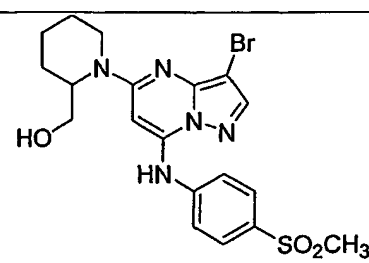


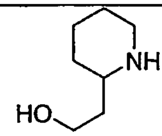
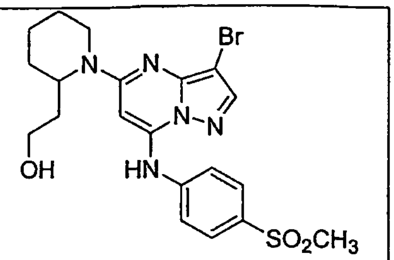
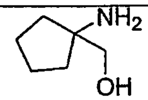
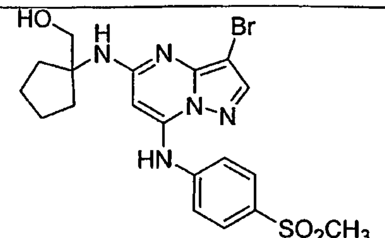
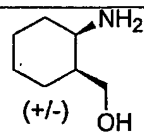
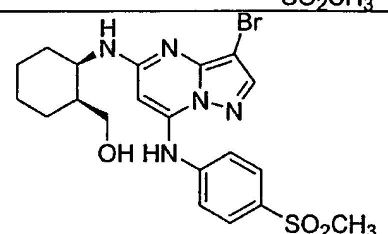
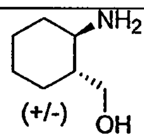
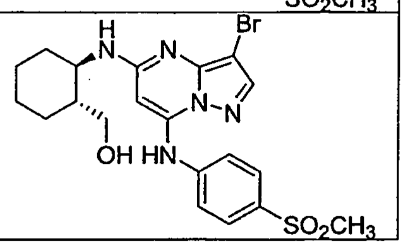
To a solution of the compound prepared in Example 21.14 (0.10 g, 0.25 mmol) and prolinol (0.12 mL, 5 eq.) and iPr_2NEt (0.22 mL, 5 eq.) was heated to reflux 24 hours. (Yield: 0.09g, 80%). MS: MH^+ = 466; m.p. = 177- 180 °C.

EXAMPLE 70-78:

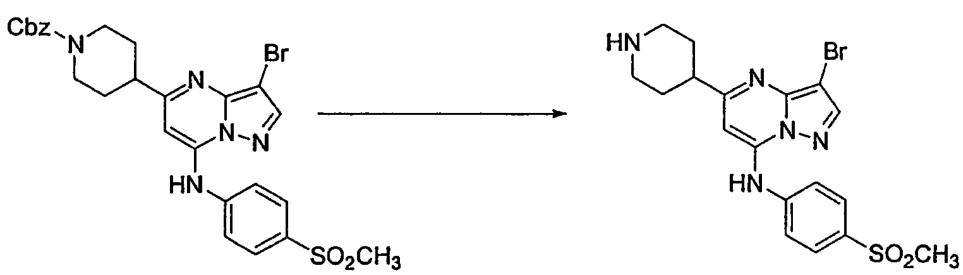
By essentially the same procedure set forth in Example 69 only substituting the amine shown in Column 2 of Table 12, the compounds shown in Column 3 of Table 12 are prepared:

TABLE 12

Ex.	Column 2	Column 3
70		
71		
72		
73		
74		

75		
76		
77		
78		

EXAMPLE 79:



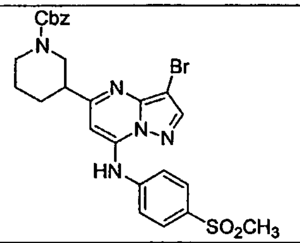
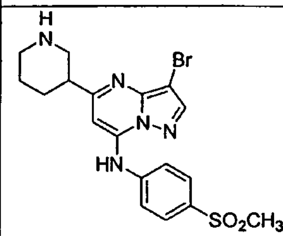
To a solution of the compound prepared in Example 21.12 in anhydrous acetonitrile is added TMSI (4 eq.), dropwise at ambient temperature. After 10 minutes the acetonitrile is removed *in vacuo*. The resulting yellow foam is treated with 2 N HCl solution (7 mL) and then washed immediately with Et_2O (5X). The pH

of the aqueous is adjusted to 10 with 50 % NaOH (aq) and the product is isolated by saturation of the solution with NaCl (s) followed by extraction with CH_2Cl_2 (5X) to give the desired product.

EXAMPLES 80:

By essentially the same procedure set forth in Example 79 only substituting the compounds shown in Column 2 of Table 13, the compounds shown in Column 3 of Table 13 are prepared.

TABLE 13

Ex.	Column 2	Column 3
80		

ASSAY:

BACULOVIRUS CONSTRUCTIONS: Cyclin E was cloned into pVL1393 (Pharmingen, La Jolla, California) by PCR, with the addition of 5 histidine residues at the amino-terminal end to allow purification on nickel resin. The expressed protein was approximately 45kDa. CDK2 was cloned into pVL1393 by PCR, with the addition of a haemaglutinin epitope tag at the carboxy-terminal end (YDVPDYAS). The expressed protein was approximately 34kDa in size.

ENZYME PRODUCTION: Recombinant baculoviruses expressing cyclin E and CDK2 were co-infected into SF9 cells at an equal multiplicity of infection (MOI=5), for 48 hrs. Cells were harvested by centrifugation at 1000 RPM for 10 minutes, then pellets lysed on ice for 30 minutes in five times the pellet volume of lysis buffer containing 50mM Tris pH 8.0, 150mM NaCl, 1% NP40, 1mM DTT and protease inhibitors (Roche Diagnostics GmbH, Mannheim, Germany). Lysates were spun down at 15000 RPM for 10 minutes and the supernatant retained. 5ml of nickel beads (for one liter of SF9 cells) were washed three times in lysis buffer (Qiagen GmbH, Germany). Imidazole was added to the baculovirus supernatant to a final concentration of 20mM, then incubated with the nickel beads for 45 minutes at 4° C. Proteins were eluted with lysis buffer containing

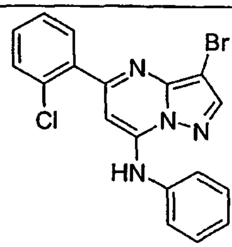
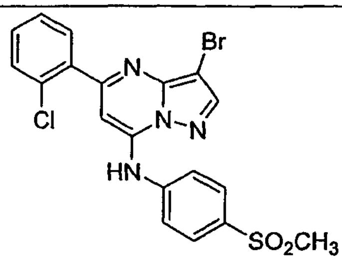
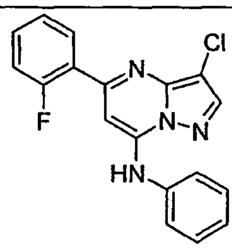
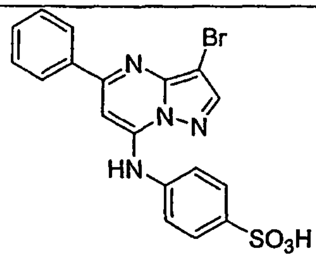
250mM imidazole. Eluate was dialyzed overnight in 2 liters of kinase buffer containing 50mM Tris pH 8.0, 1mM DTT, 10mM MgCl2, 100uM sodium orthovanadate and 20% glycerol. Enzyme was stored in aliquots at -70^{o}C.

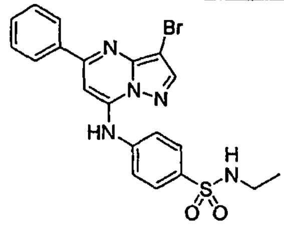
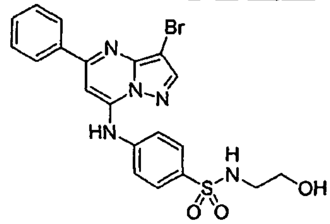
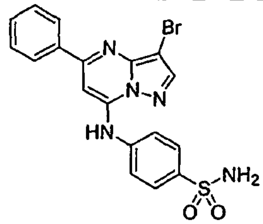
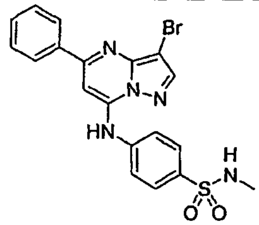
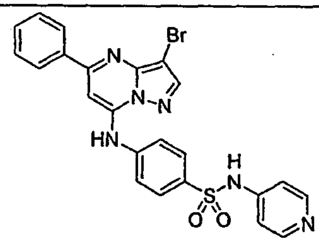
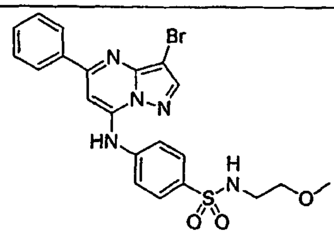
IN VITRO KINASE ASSAY: Cyclin E/CDK2 kinase assays were performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme was diluted to a final concentration of 50 μg/ml in kinase buffer containing 50mM Tris pH 8.0, 10mM $MgCl_2$, 1mM DTT, and 0.1mM sodium orthovanadate. The substrate used in these reactions was a biotinylated peptide derived from Histone H1 (from Amersham, UK). The substrate was thawed on ice and diluted to 2 μM in kinase buffer. Compounds were diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 μl of the 50 μg/ml enzyme solution (1 μg of enzyme) and 20 μl of the 2 μM substrate solution were mixed, then combined with 10 μl of diluted compound in each well for testing. The kinase reaction was started by addition of 50 μl of 2 μM ATP and 0.1 μCi of 33P-ATP (from Amersham, UK). The reaction was allowed to run for 1 hour at room temperature. The reaction was stopped by adding 200 μl of stop buffer containing 0.1% Triton X-100, 1mM ATP, 5mM EDTA, and 5 mg/ml streptavidine coated SPA beads (from Amersham, UK) for 15 minutes. The SPA beads were then captured onto a 96-well GF/B filter plate (Packard/Perkin Elmer Life Sciences) using a Filtermate universal harvester (Packard/Perkin Elmer Life Sciences.). Non-specific signals were eliminated by washing the beads twice with 2M NaCl then twice with 2 M NaCl with 1% phosphoric acid. The radioactive signal was then measured using a TopCount 96 well liquid scintillation counter (from Packard/Perkin Elmer Life Sciences).

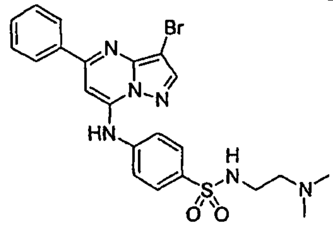
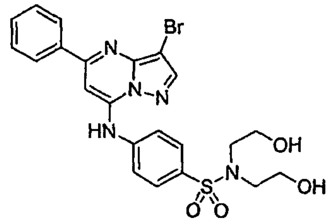
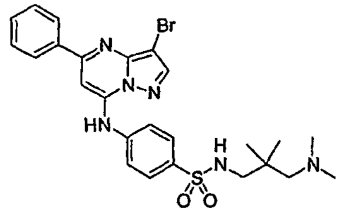
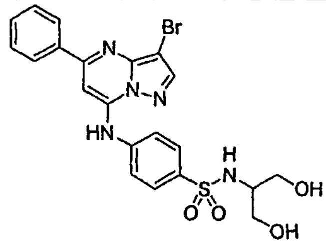
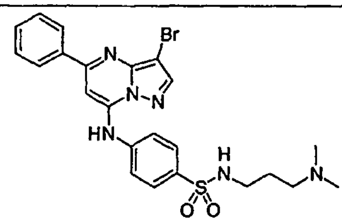
IC_{50} DETERMINATION: Dose-response curves were be plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory compounds. Concentration of compound was plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated samples. To generate IC_{50} values, the dose-response curves were then fitted to a standard sigmoidal curve and IC_{50} values were derived by nonlinear regression

analysis. The thus-obtained IC_{50} values for some of the compounds of the invention are shown in **Table 14.**

Table 14

Compound	Example	IC_{50} (μM)
	2	0.51
	1	0.4 1.4
	3	0.042
	22	0.082

	28	0.080
	30	0.029
	31	0.045
	32	0.057
	38	0.040
	42	0.070

	43	0.034
	47	0.034
	48	0.025
	50	0.030
	53	0.011

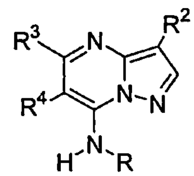
As demonstrated above by the assay values, the compounds of the present invention exhibit excellent CDK inhibitory properties.

While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

CLAIMS

What is claimed is:

1. A compound represented by the structural formula:

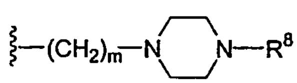
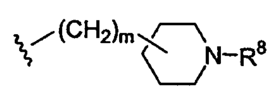
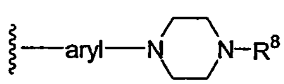


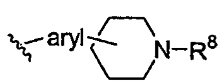
Formula I

or a pharmaceutically acceptable salt or solvate of said compound, wherein:

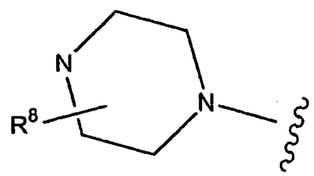
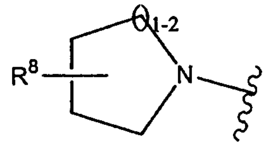
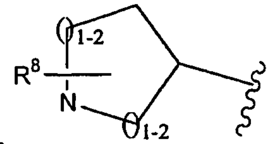
R is an unsubstituted aryl or aryl substituted with one or more moieties which moieties can be the same or different, each moiety being independently selected from the group consisting of halogen, CN, $-OR^5$, SR^5, $-CH_2OR^5$, $-C(O)R^5$, $-SO_3H$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)NR^5R^6$, $-CF_3$, $-OCF_3$ and heterocyclyl;

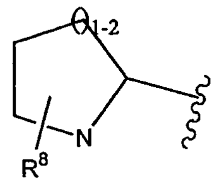
R^2 is selected from the group consisting of R^9, alkyl, alkynyl, alkynylalkyl, cycloalkyl, $-CF_3$, $-C(O_2)R^6$, aryl, arylalkyl, heteroarylalkyl, heterocyclyl, alkyl substituted with 1-6 R^9 groups which groups can be the same or different with each R^9 being independently selected, aryl substituted with 1-3 aryl or heteroaryl groups which can be the same or different and are independently selected from phenyl, pyridyl, thiophenyl, furanyl and thiazolo groups,

, ,  and

;

R^3 is selected from the group consisting of H, halogen, $-NR^5R^6$, $-C(O)NR^5R^6$, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl,

, ,  and



wherein each of said alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl for R^3 and the heterocyclyl moieties whose structures are shown immediately above for R^3 can be substituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-(CR^4R^5)_nOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_nNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$;

R^4 is H, halo or alkyl;

R^5 is H or alkyl;

R^6 is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-N(R^5)Boc$, $-(CR^4R^5)_nOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

R^{10} is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being

independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^4R^5$, $-N(R^5)Boc$, $-(CR^4R^5)_nOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^4R^5$;

or optionally (i) R^5 and R^{10} in the moiety $–NR^5R^{10}$, or (ii) R^5 and R^6 in the moiety $–NR^5R^6$, may be joined together to form a cycloalkyl or heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with one or more R^9 groups;

R^7 is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ and $-N(R^5)C(O)NR^5R^{10}$;

R^8 is selected from the group consisting of R^6, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$ and $–S(O_2)R^7$;

R^9 is selected from the group consisting of halogen, CN, $-NR^5R^{10}$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $–N(R^5)C(O)NR^5R^{10}$;

m is 0 to 4, and

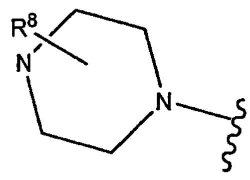
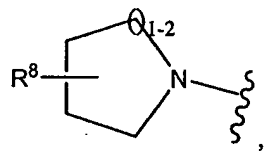
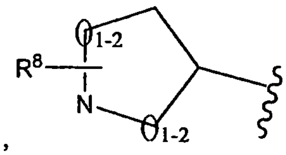
n is 1 to 4,

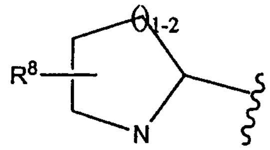
with the following provisos: (i) that when R is an unsubstituted phenyl, then R^2 is not alkyl, $-C(O_2)R^6$, aryl or cycloalkyl, and (ii) that when R is a phenyl substituted with a hydroxyl group, then R^2 is halogen only.

2. The compound of claim 1, wherein R is an unsubstituted aryl or aryl substituted with one or moieties which moieties can be the same or different with each moiety being independently selected from the group consisting of halogen, CN, $-OR^5$, $-S(O_2)NR^5R^6$, $-SO_3H$, CH_2OR^5, $-S(O_2)R^6$, $-C(O)NR^5R^6$, $-CF_3$, $-OCF_3$ and heterocyclyl.

R^2 is R^2 is halogen, CF_3, CN, lower alkyl and cycloalkyl;

R^3 is H, unsubstituted aryl, unsubstituted heteroaryl, aryl substituted with one or more moieties selected from the group consisting of halogen, CN, $-OR^5$, CF_3, $-OCF_3$, lower alkyl and cycloalkyl, heterocyclyl, heteroaryl substituted with one or more moieties selected from the group consisting of halogen, CN, $-OR^5$, CF_3, $-OCF_3$, alkyl and cycloalkyl,

, ,  and



R^4 is H or lower alkyl;

R^5 is H or lower alkyl;

m is 0 to 2; and

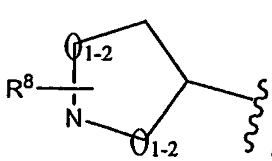
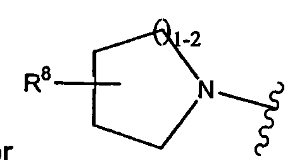
n is 1 or 2.

3. The compound of claim 2, wherein R is an unsubstituted phenyl.

4. The compound of claim 2, wherein R is phenyl substituted with one or more moieties selected from the group consisting of F, Cl, Br, CN, $-SO_3H$, $-S(O_2)NR^5R^6$, $-S(O_2)CH_3$, $-NR^5R^{10}$, -OH, hydroxymethyl, CF_3 and morpholinyl.

5. The compound of claim 2, wherein R^2 is F, Cl, Br, CF_3, lower alkyl and cycloalkyl.

6. The compound of claim 2, wherein R^3 is H, lower alkyl, unsubstituted aryl, aryl substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Cl, Br, CF_3, lower alkyl, methoxy, and CN, or

 or .

7. The compound of claim 6, wherein said lower alkyl is methyl, ethyl, isopropyl or tert-butyl.

8. The compound of claim 2, wherein R^4 is H.

9. The compound of claim 2, wherein R^5 is H.

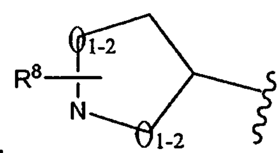
10. The compound of claim 2, wherein m is 0.

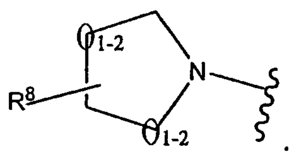
11. The compound of claim 2, wherein R is 4-(methylsulfonyl)phenyl.

12. The compound of claim 2, wherein R^2 is Cl, Br, isopropyl, ethyl, cyclopropyl, cyclobutyl or cyclopentyl.

13. The compound of claim 6, wherein R^3 is unsubstituted phenyl, or phenyl substituted with $-S(O_2)NR^5R^6$.

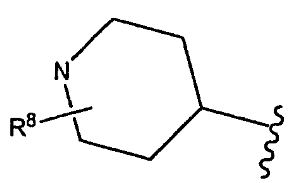
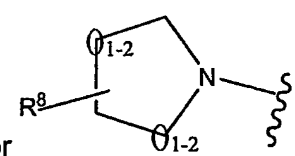
14. The compound of claim 6, wherein R^3 is tert-butyl or isopropyl.

15. The compound of claim 6, wherein R^3 is 2-fluorophenyl, 2-chlorophenyl, 2,3-dichlorophenyl, 2-methylphenyl, 2-methoxyphenyl,  or

.

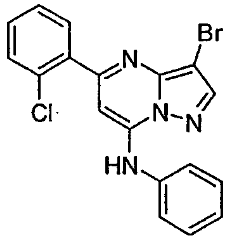
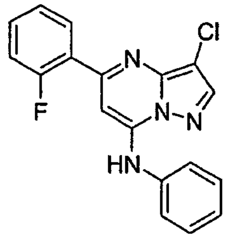
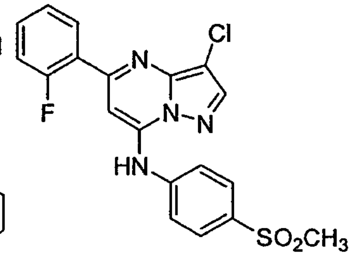
16. The compound of claim 6, wherein R^3 is 3-(trifluoromethyl)phenyl.

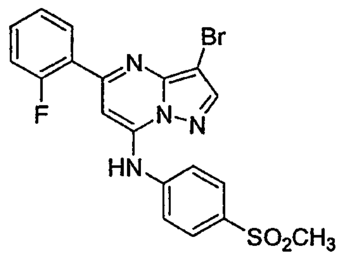
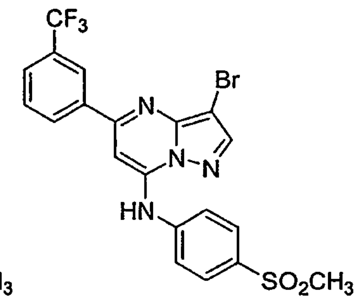
17. The compound of claim 15, wherein R^3 is:

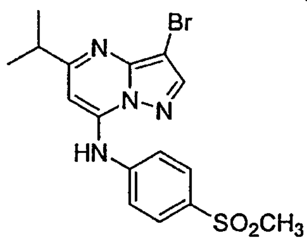
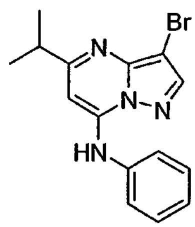
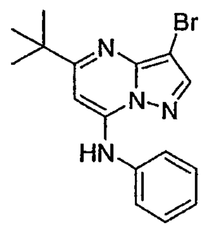
 or .

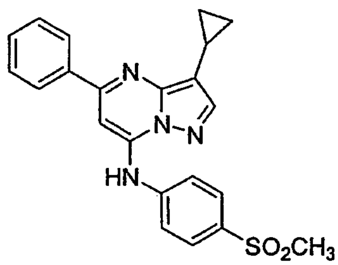
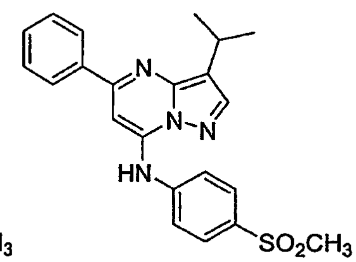
18. The compound of claim 17, wherein R^8 is $(CH_2)_nOH$ or $(CH_2)_nOCH_3$, where n is 1 or 2.

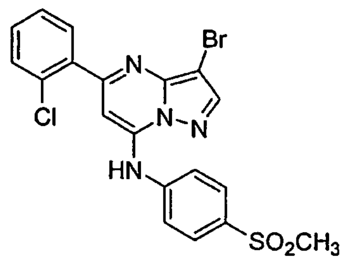
19. A compound selected from the group consisting of:

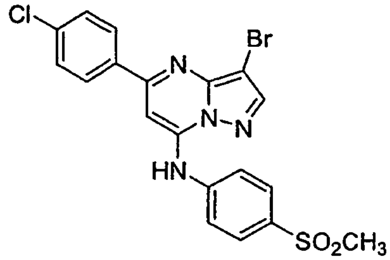




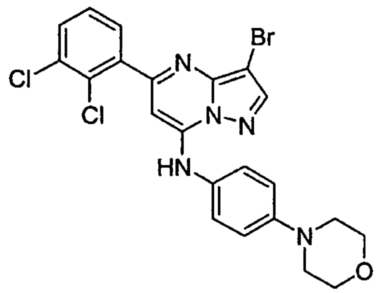



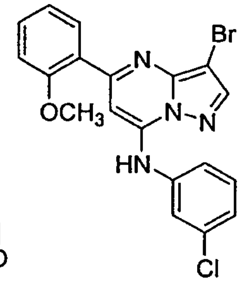




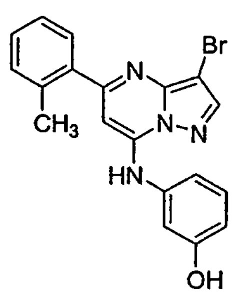



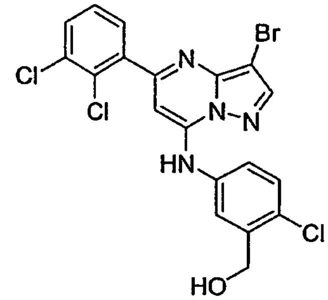


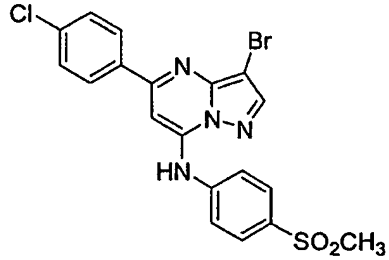


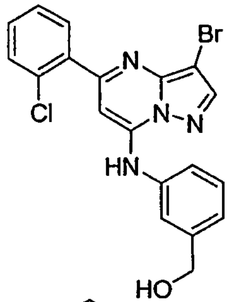
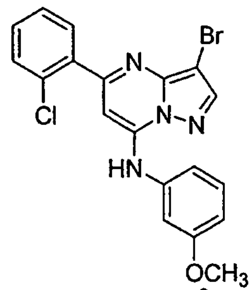
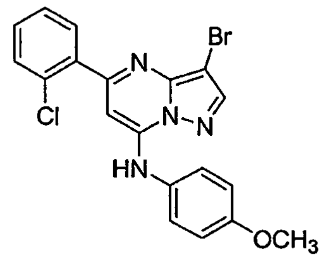


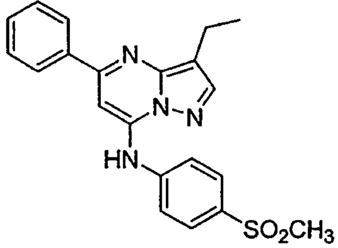
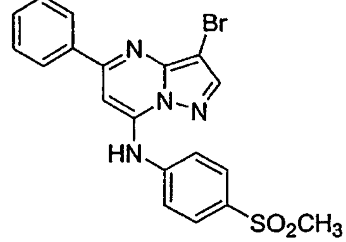


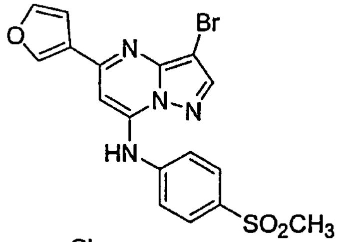
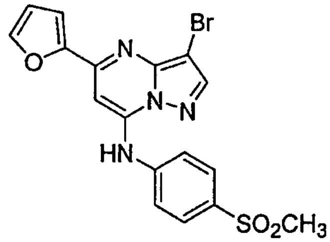
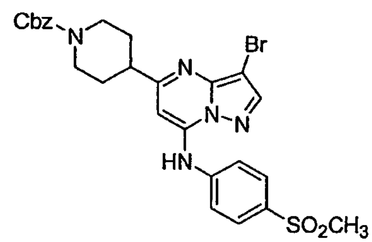


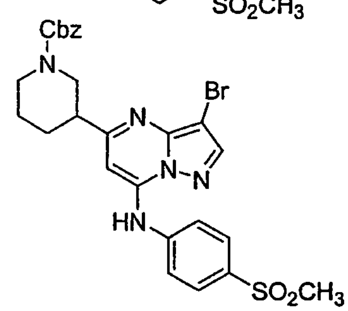
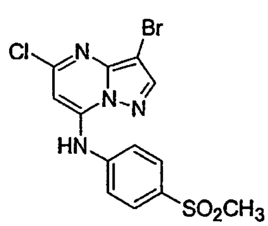
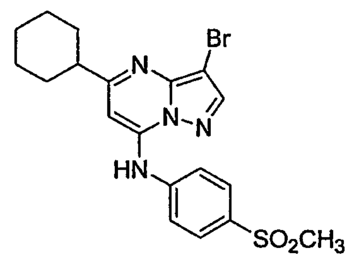


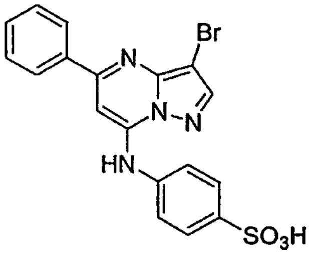
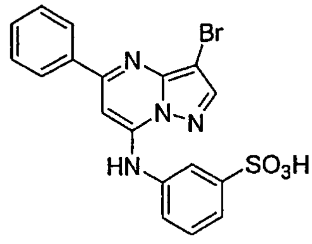
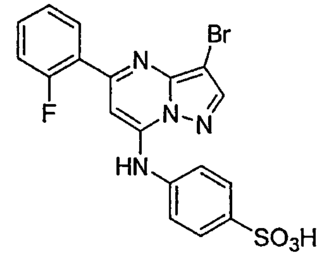
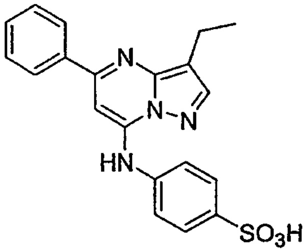
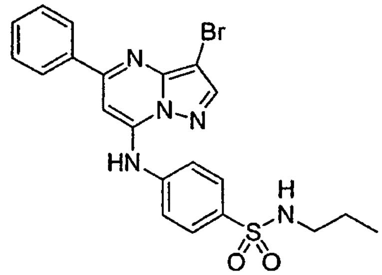
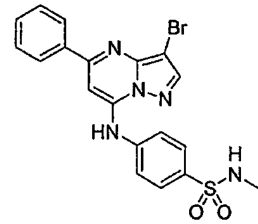
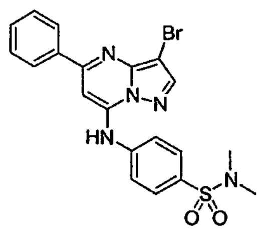
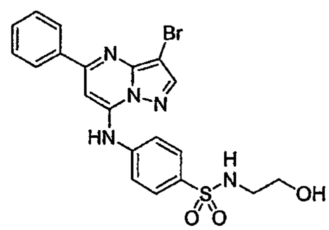
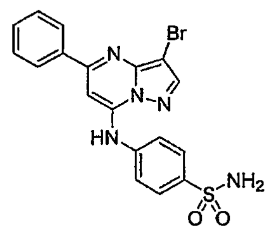
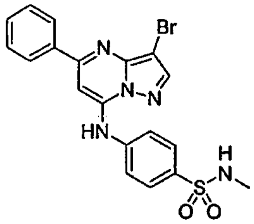
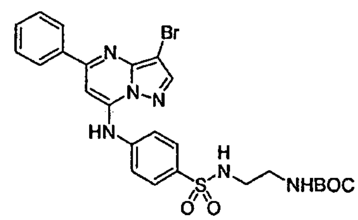
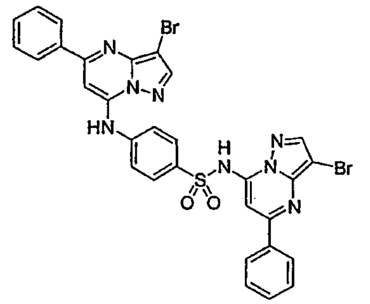
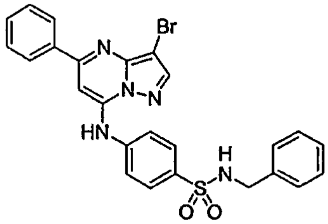
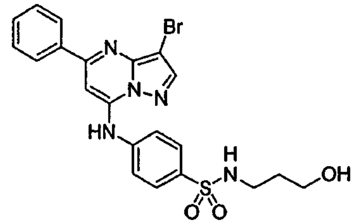
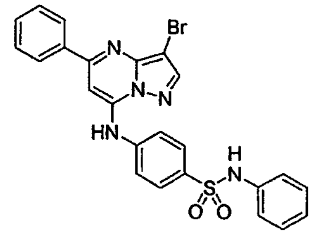
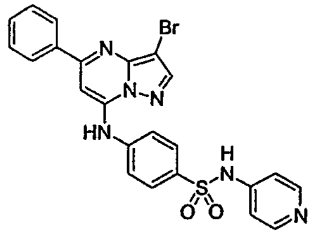
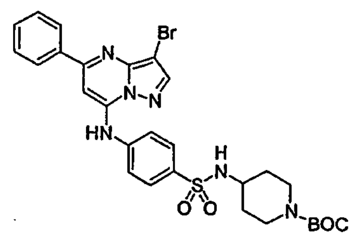
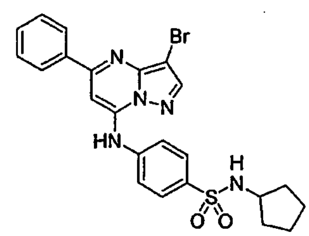


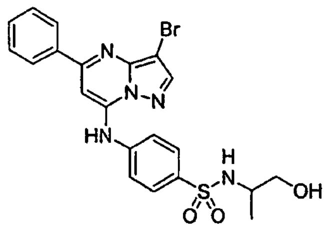




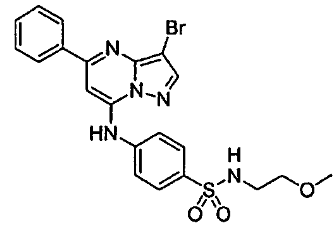



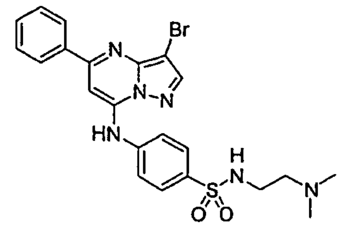




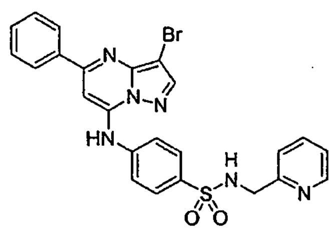




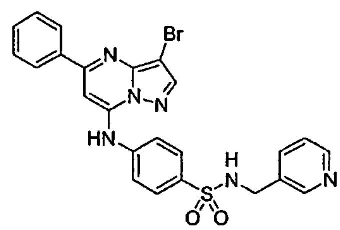



















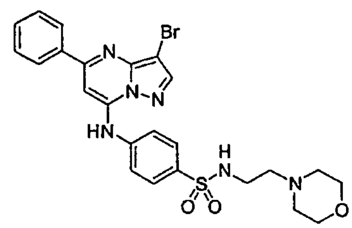


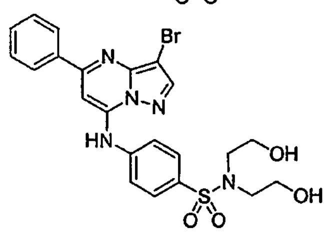


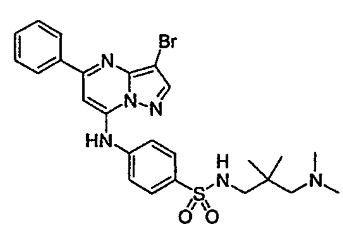


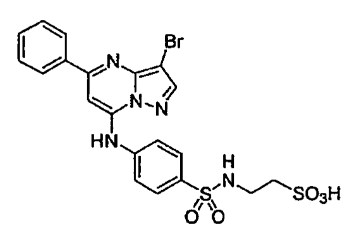


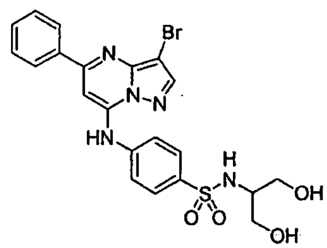


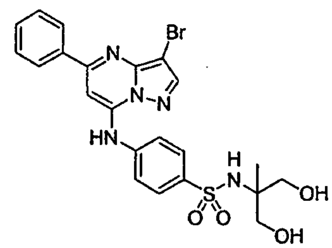


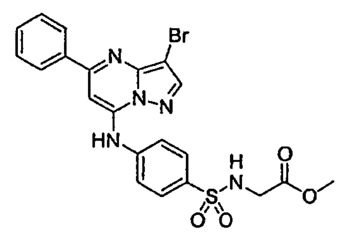


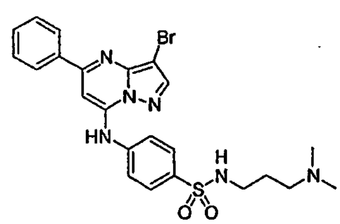


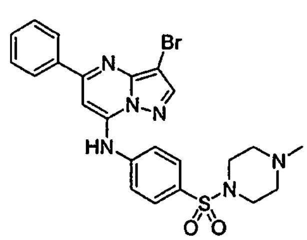


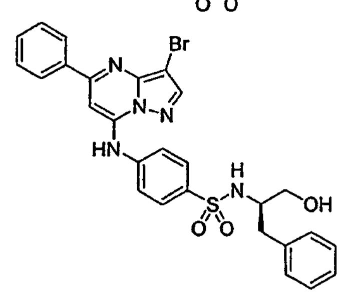


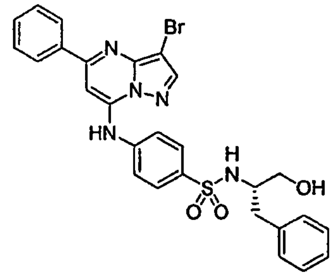


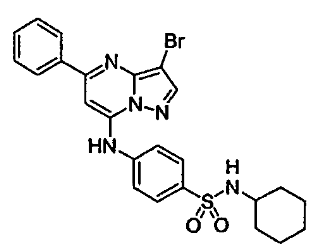


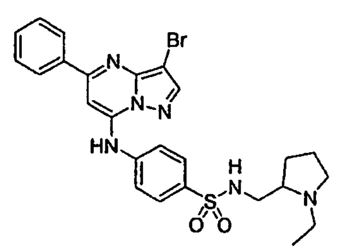


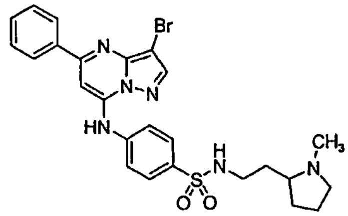
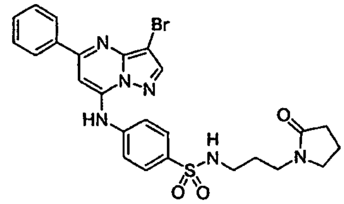
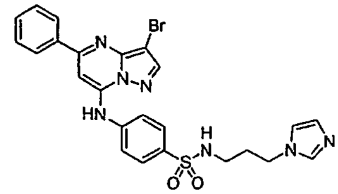
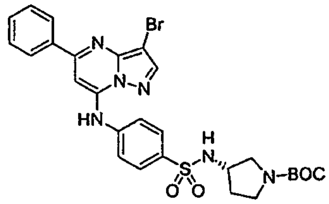
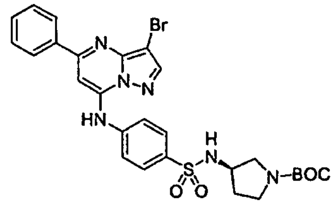
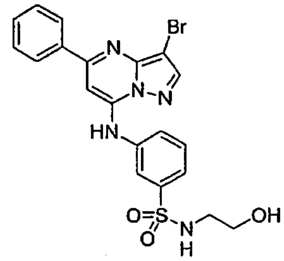
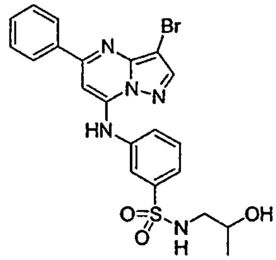
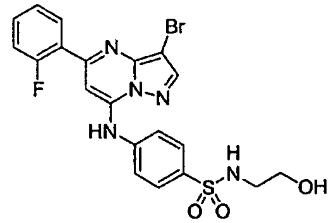
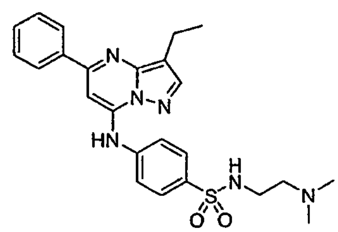
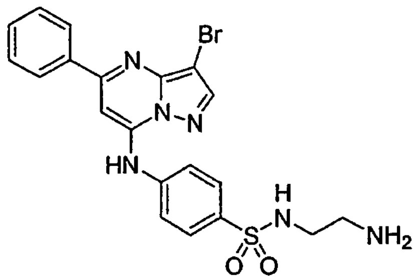
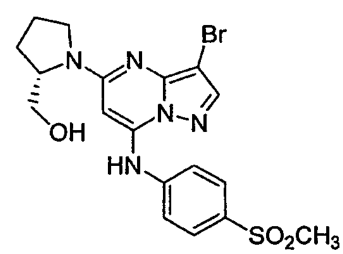
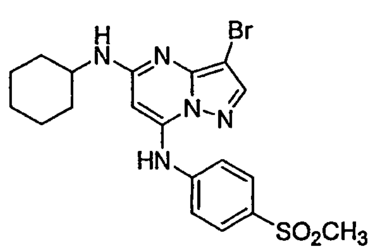
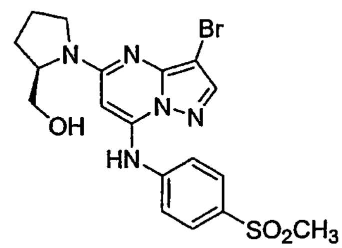
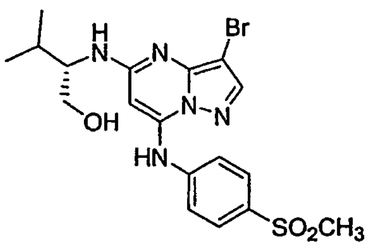
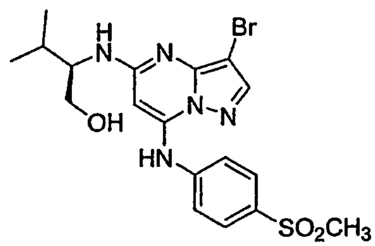


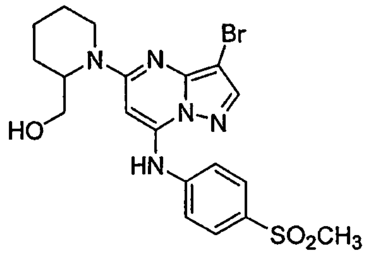


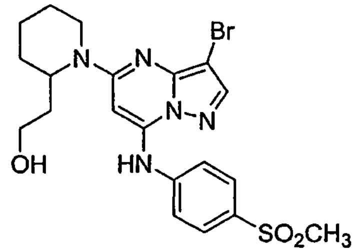


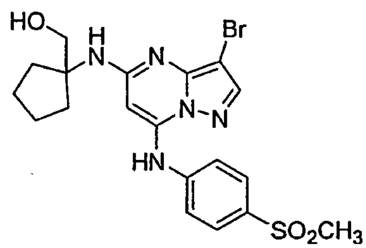


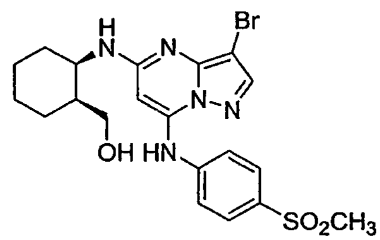


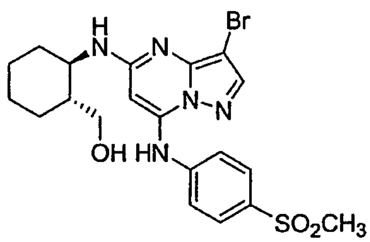
















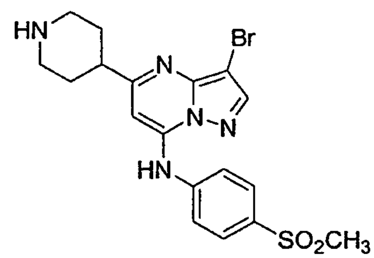


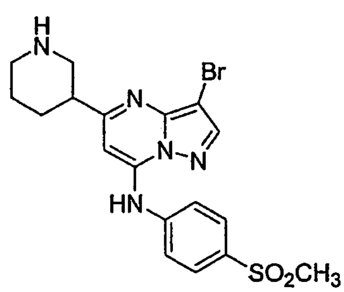






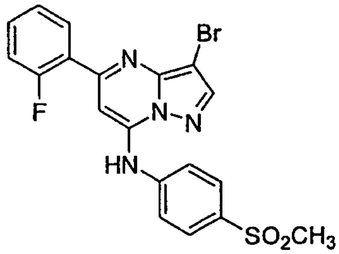
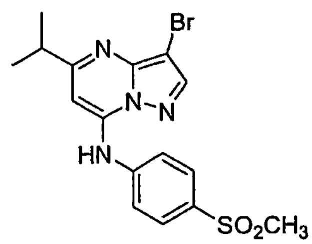
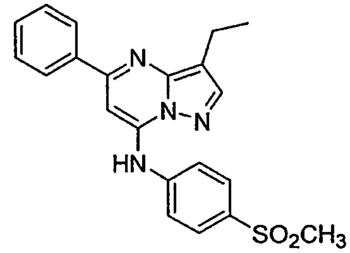
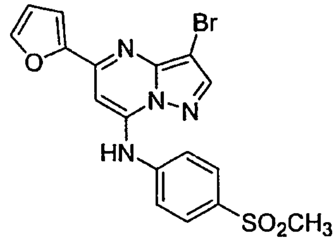
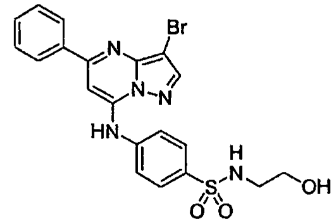
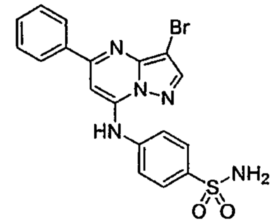
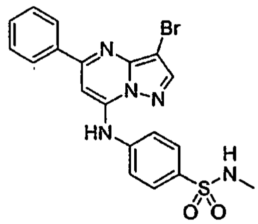
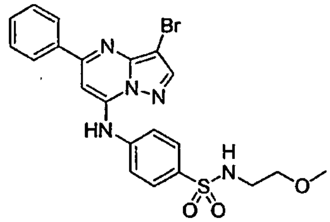
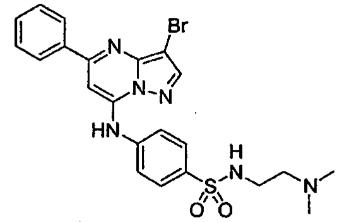
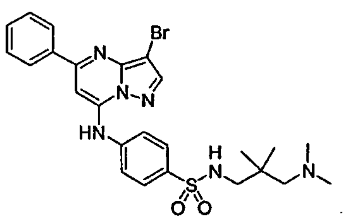
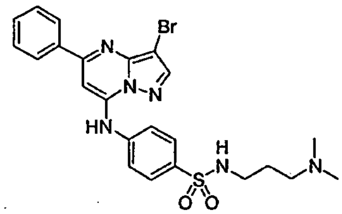
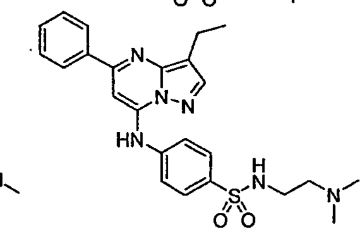
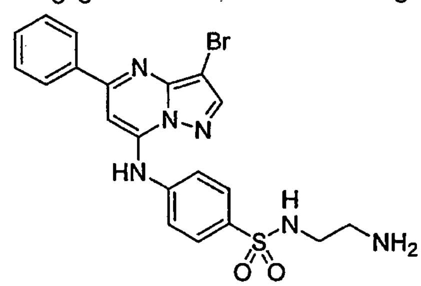
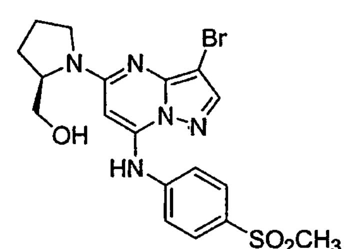
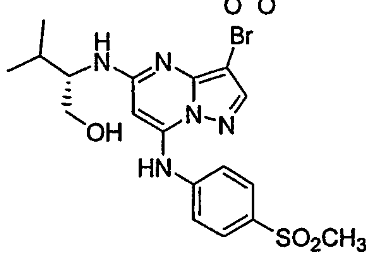
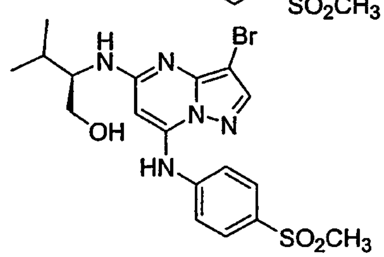


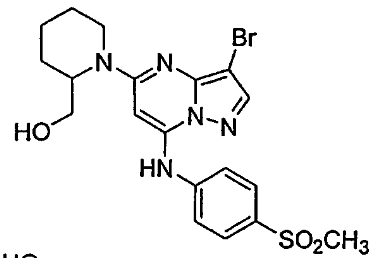
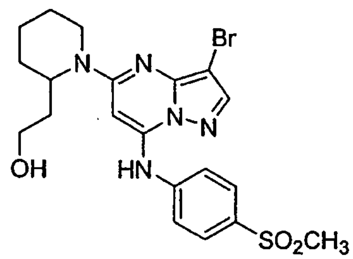
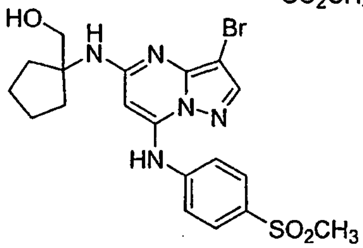
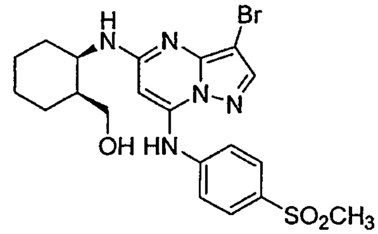
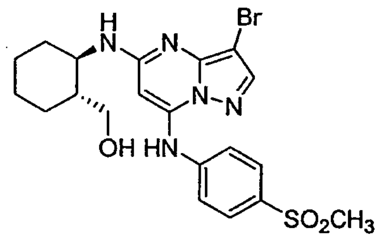
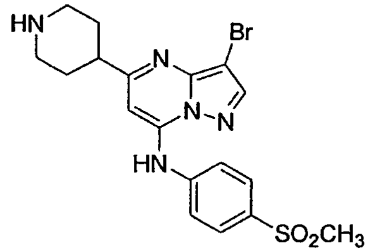




or a pharmaceutically acceptable salt or solvate thereof.

20. A compound of the formula: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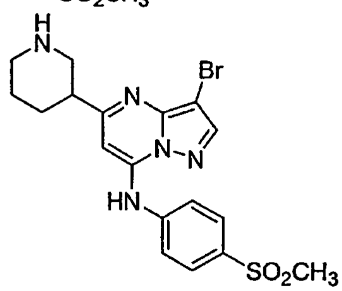

or a pharmaceutically acceptable salt or solvate thereof.

21. A method of inhibiting one or more cyclin dependent kinases, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such inhibition.

22. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such treatment.

23. The method of claim 22, wherein said cyclin dependent kinase is CDK2.

24. The method of claim 22, wherein said disease is selected from the group consisting of: cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid,

prostate, and skin, squamous cell carcinoma; leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T- cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, Burkett's lymphoma; acute and chronic myelogenous leukemia, myelodysplastic syndrome, promyelocytic leukemia; fibrosarcoma, rhabdomyosarcoma; astrocytoma, neuroblastoma, glioma and schwannomas; melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

25. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering to a mammal in need of such treatment

an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof;

and

an amount of at least one second compound, said second compound being an anti-cancer agent;

wherein the amounts of the first compound and said second compound result in a therapeutic effect.

26. The method of claim 25, further comprising radiation therapy.

27. The method of claim 25, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan (or CPT-11), camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, 5-Fluorouracil, temozolomide, cyclophosphamide, 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl-]-1-piperidinyl]-2-oxoehtyl]-1-piperidinecarboxamide, tipifarnib, L778,123 (a farnesyl protein transferase inhibitor), BMS 214662 (a farnesyl protein transferase inhibitor), Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin,

Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

28. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 in combination with at least one pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, additionally comprising one or more anti-cancer agents selected from the group consisting of cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, 5-fluorouracil, temozolomide, cyclophosphamide, 4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl-]-1-piperidinyl]-2-oxoehtyl]-1-piperidinecarboxamide, Zarnestra® (tipifarnib), L778,123 (a farnesyl protein transferase inhibitor), BMS 214662 (a farnesyl protein transferase inhibitor), Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene,

Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

30. A compound of claim 1, in isolated and purified form.